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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 295/116, 295/145, A61K 31/445, 31/449, C07D 401/10, 401/14, 403/10, 407/04, 409/14, 413/10

A2

(11) International Publication Number: WO 96/26196

(43) International Publication Date: 29 August 1996 (29.08.96)

(21) International Application Number: PCT/US96/01532

(22) International Filing Date: 16 February 1996 (16.02.96)

(30) Priority Data:
08/392,697 23 February 1995 (23.02.95) US
08/457,712 2 June 1995 (02.06.95) US

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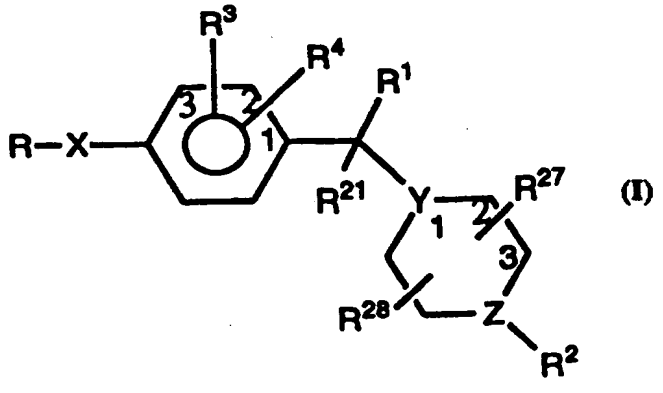
(81) Designated States: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: BENZYLPIPERIDINES AND PIPERAZINES AS MUSCARINIC ANTAGONISTS

(57) Abstract

Di-N-substituted piperazine or 1,4 di-substituted piperadine compounds in accordance with formula (I) (including all isomers, salts, esters, and solvates) wherein R, R^1, R^2, R^3, R^4, R^{21}, R^{27}, R^{28}, X, Y, and Z are as defined herein are muscarinic antagonists useful for treating cognitive disorders such as Alzheimer's disease. Pharmaceutical compositions and methods of preparation are also disclosed. Also disclosed are synergistic combinations of compounds of the above formula or other compounds capable of enhan cing acetylcholine release with acetylcholinesterase inhibitors.



(I)

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BENZYLPIPERIDINES AND PIPERAZINES AS MUSCARINIC ANTAGONISTS

BACKGROUND OF THE INVENTION

The present invention relates to di-N-substituted piperazines and 1,4-di-substituted piperidines useful in the treatment of cognitive disorders, pharmaceutical compositions containing the compounds, methods of treatment using the compounds, and to the use of said compounds in combination with acetylcholinesterase inhibitors.

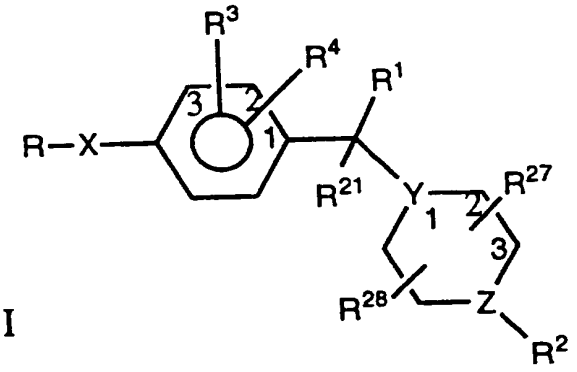
Alzheimer's disease and other cognitive disorders have received much attention lately, yet treatments for these diseases have not been very successful. According to Melchiorre et al. (J. Med. Chem. (1993), 36, 3734-3737), compounds that selectively antagonize M2 muscarinic receptors, especially in relation to M1 muscarinic receptors, should possess activity against cognitive disorders. Baumgold et al. (Eur. J. of Pharmacol., 251, (1994) 315-317) disclose 3-α-chloroimperialine as a highly selective m2 muscarinic antagonist.

The present invention is predicated on the discovery of a class of di-N-substituted piperazines and 1,4-di-substituted piperidines, some of which have m2 selectivity even higher than that of 3-α-chloroimperialine. Logemann et al (Brit. J. Pharmacol. (1961), 17, 286-296) describe certain di-N-substituted piperazines, but these are different from the inventive compounds of the present

invention. Furthermore, the compounds of Logemann et al. are not disclosed to have activity against cognitive disorders.

SUMMARY OF THE INVENTION

The present invention relates to compounds according to the structural formula I,

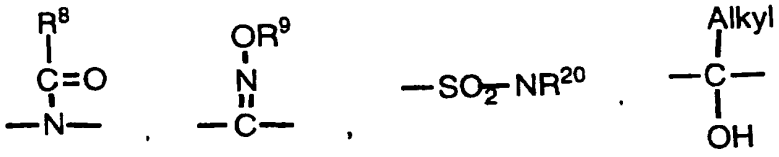


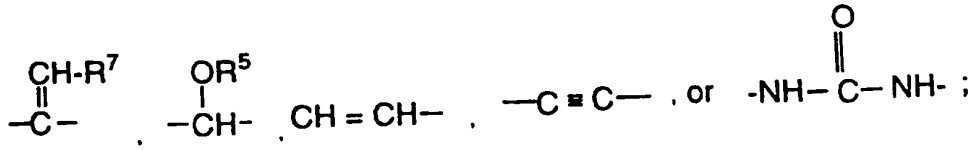
I

including all isomers and pharmaceutically acceptable salts, esters, and solvates thereof,

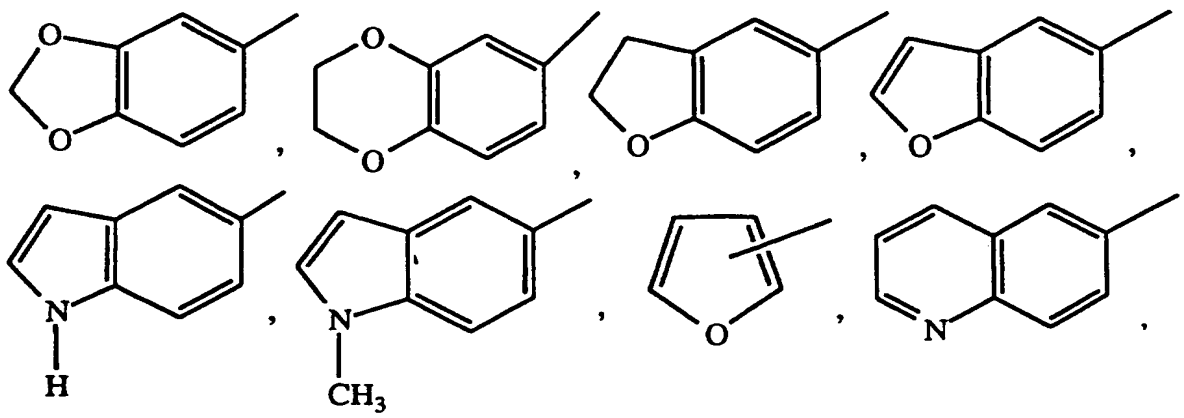
wherein one of Y and Z is N and the other is N, CH, or C-alkyl;

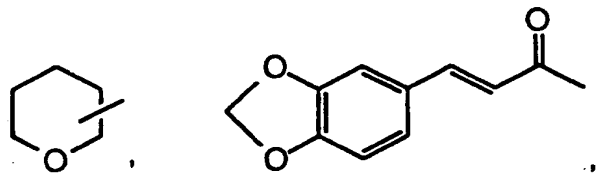
X is -O-, -S-, -SO-, -SO_2-, -NR^6-, -CO-, -CH_2-, -CS-, -$C(OR^5)_2$-, -$C(SR^5)_2$-, -$CONR^{20}$-, -C(alkyl)2-, -C(H)(alkyl)-, -NR^{20}-SO_2-, -$NR^{20}CO$-,

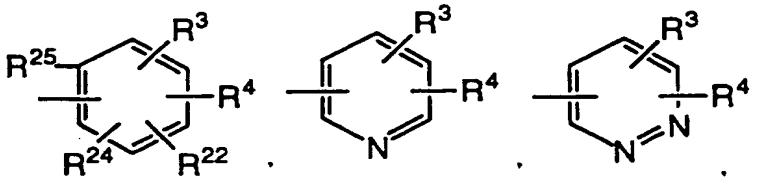


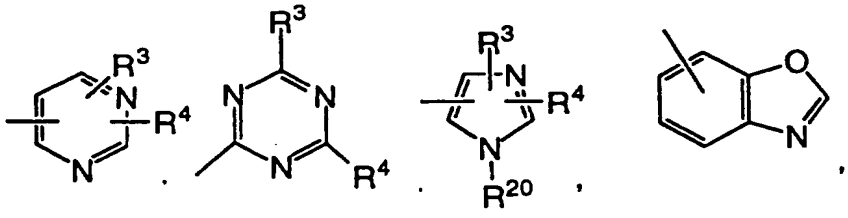


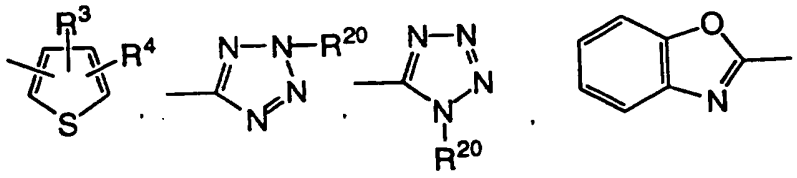
R is

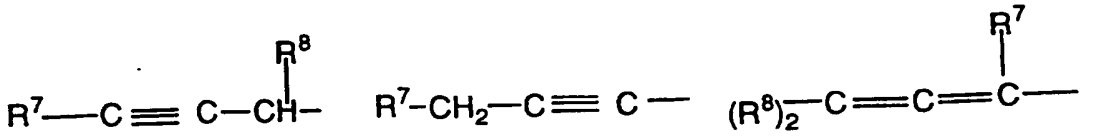


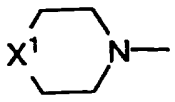




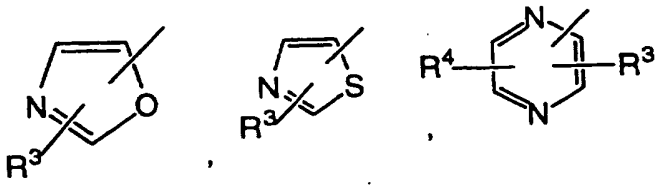


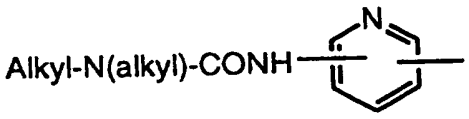






(wherein X^1 is $-CH_2-$, -O-, or $-NR^7-$),

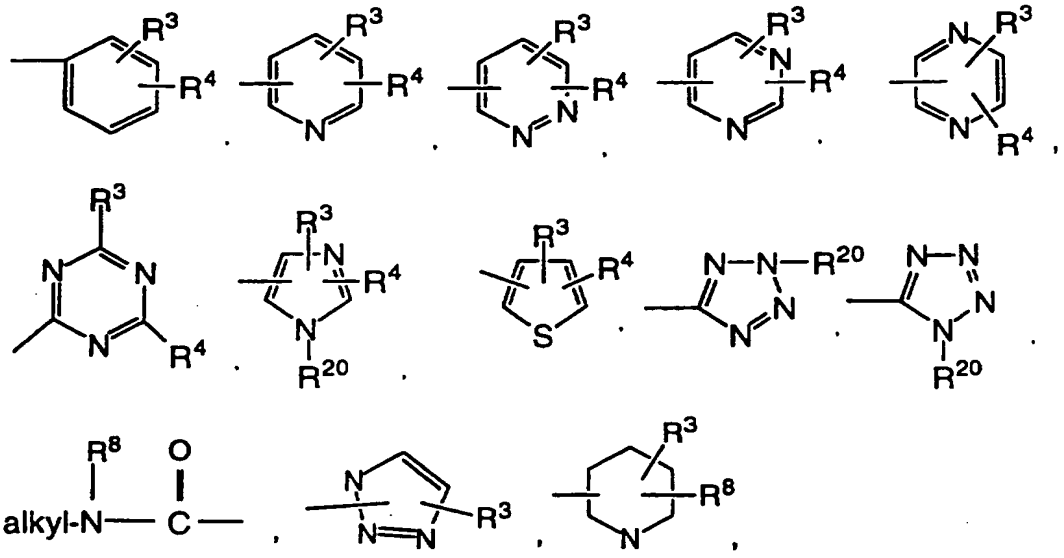




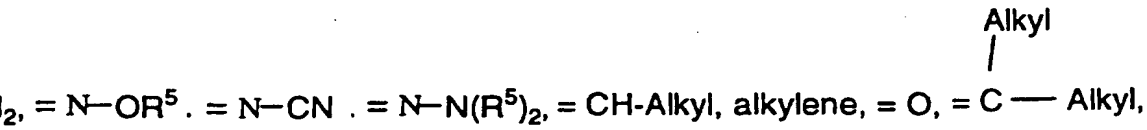
hydrogen, acyl, alkyl, alkenyl, cycloalkyl, cycloalkyl substituted with up to two alkyl groups, cycloalkenyl, bicycloalkyl, arylalkenyl, benzyl, benzyl substituted with up to three independently selected R^3 groups, cycloalkylalkyl, polyhaloacyl, benzyloxyalkyl, hydroxyC_2-C_{20}alkyl, alkenylcarbonyl, alkylarylsulfonyl, alkoxycarbonylaminoacyl, alkylsulfonyl, or arylsulfonyl, additionally, when X is $-CH_2-$, R may also be -OH; in further addition, when X is not N, R may also be hydroxymethyl, in further addition, R and X may combine to

form the group Prot-(NOAA)$_r$-NH- wherein r is an integer of 1 to 4, Prot is a nitrogen protecting group and when r is 1, NOAA is a naturally occuring amino acid or an enantiomer thereof, or when r is 2 to 4, each NOAA is a peptide of an independently selected naturally occuring amino acid or an enantiomer thereof;

R^1 and R^{21} are independently selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkyl, alkynyl, cyano, aminoalkyl, alkoxycarbonyl, aminocarbonyl, hydroxyguanidino, alkoxycarbonylalkyl, phenyl alkyl, alkylcarbonlyoxyalkyl,

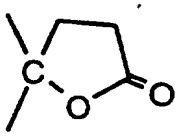


H, —OH, (provided R^1 and R^{21} are both not —OH and Y is not N), formyl, —CO alkyl, -COacyl, —COaryl, and hydroxyalkyl; additionally R^1 and R^{21} together may form the group



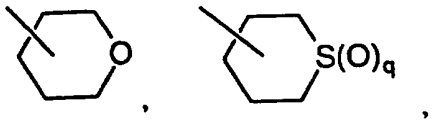
$=CH_2$, $=N-OR^5$. $=N-CN$. $=N-N(R^5)_2$, $=CH$-Alkyl, alkylene, $=O$, $=C(\text{Alkyl})-\text{Alkyl}$,

$=C(halo)_2$, in further addition, R^1 and R^{21} together with the carbon atom to which they are attached may form the group

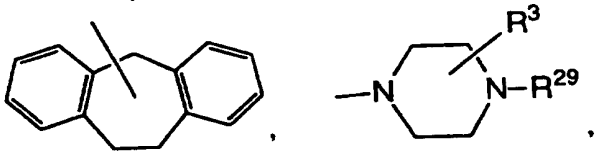


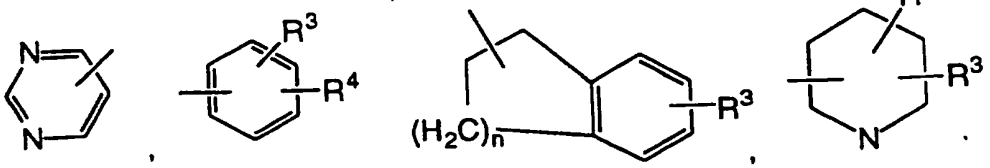
or R^1 and R^{21} together with the carbon atom to which they are attached may form a saturated heterocyclic ring containing 3 to 7 carbon atoms and one group selected from S, O, and NH;

R^2 is H, alkyl, alkenyl, cycloalkyl, cycloalkyl substituted with 1 to 3 independently selected R^3 groups, cycloalkenyl, hydroxyC_2-C_{20}alkyl, alkynyl, alkylamide, cycloalkylalkyl, hydroxyarylalkyl, bicycloalkyl, alkynyl, acylaminoalkyl, arylalkyl, hydroxyalkoxyalkyl, azabicyclo, alkylcarbonyl. alkoxyalkyl, aminocarbonylalkyl, alkoxycarbonylaminoalkyl, alkoxycarbonylamino(alkyl)alkyl; alkylcarbonyloxyalkyl, arylhydroxyalkyl, alkylcarbonylamino(alkyl)alkyl, dialkylamino,

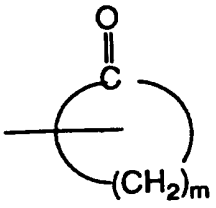


(wherein q is an integer of 0 to 2)

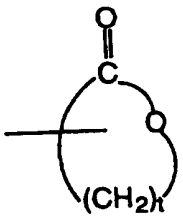




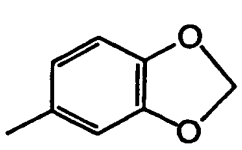
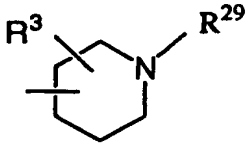
wherein n is 1-3



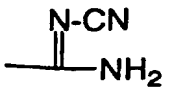
wherein m is an integer of 4 to 7,



wherein t is an integer of 3 to 5,

(wherein R^{29} is H, alkyl, acyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylsulfonyl, arylsulfonyl),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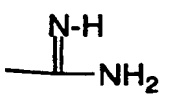
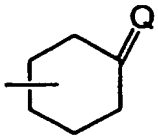



(wherein Q is O, NOH, or NO-alkyl), or when Z is -CH-, R^2 may also be alkoxycarbonyl, hydroxymethyl, $-N(R^8)_2$;

R^3, R^4, R^{22}, R^{24}, and R^{25} are independently selected from the group consisting of H, halo, alkoxy, benzyloxy, benzyloxy substituted by nitro or aminoalkyl, haloalkyl, polyhaloalkyl, nitro, cyano, sulfonyl, hydroxy, amino, alkylamino, formyl, alkylthio, polyhaloalkoxy, acyloxy, trialkylsilyl, alkylsulfonyl, arylsulfonyl, acyl, alkoxycarbonyl alkylsulfinyl; $-OCONH_2$, -OCONH-alkyl, $-OCON(alkyl)_2$, -NHCOO-alkyl, -NHCO-alkyl, phenyl, hydroxyalkyl, or morpholino;

each R^5 and R^6 is independently selected from the group consisting of H and alkyl, provided that when X is $C(OR^5)_2$ or $C(SR^5)_2$, both R^5 groups cannot be H, and in addition, when X is $C(OR^5)_2$ or $C(SR^5)_2$, the two R^5 groups in X may be joined to form $—(CH_2)_p-$ wherein p is an integer of 2 to 4;

R^7 is independently selected from the group consisting of H, alkyl, arylalkyl, cycloalkyl, aryl and aryl substituted with R^3 and R^4 as defined herein;

each R^8 is independently selected from the group consisting of H, hydroxyalkyl, or alkyl or two R^8 groups may be joined to form an alkylene group;

R^9 is H, alkyl, or acyl:

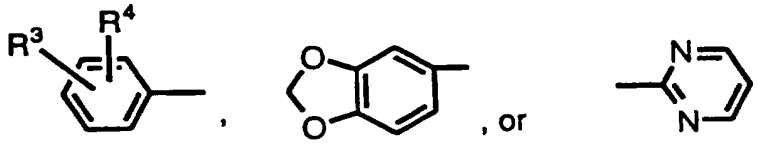
R^{20} is H, phenyl or alkyl; and

R^{27} and R^{28} are independently selected from the group consisting of H, alkyl, hydroxyalkyl, arylalkyl, aminoalkyl, haloalkyl, thioalkyl, alkylthioalkyl, carboxyalkyl, imidazolyalkyl, and indolyalkyl, additionally R^{27} and R^{28} may combine to form an alkylene group..

In a preferred group of compounds Y and Z are N

In another preferred group of compounds Y is CH and Z is N

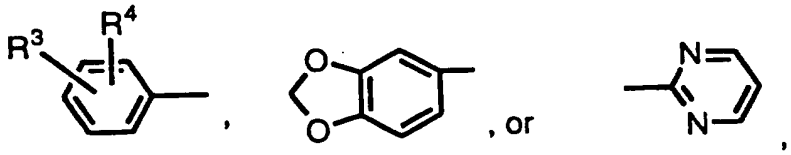
In another preferred group of compounds R is



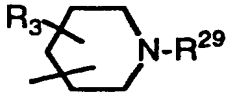
and X is O, SO or SO_2.

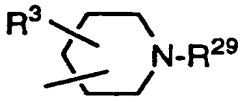
In another preferred group of compounds R^3 and R^4 are H and either R^1 is cycloalkyl, alkyl, or CN and R^{21} is H or R^1 and R^{21} together form $=CH_2$ or =O.

In another preferred group of compounds R is



X is O , SO or SO_2, R^3 and R^4 are H and either R^1 is cycloalkyl, alkyl, or CN and R^{21} is H or R^1 and R^{21} together form $=CH_2$ or =O.

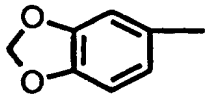
In another preferred group of compounds Y and Z are N, R^1 is cycloalkyl, alkyl or CN, R^{21} is H and R^2 is cycloalkyl or  .

In another preferred group of compounds Y is CH, Z is N, and R^2 is cycloalkyl or  .

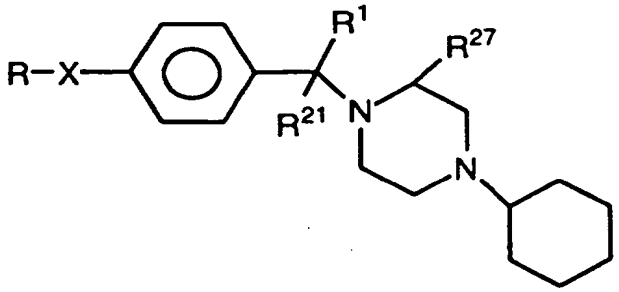
In another preferred group of compounds at least one of R^{27} and R^{28} is alkyl.

In another preferred group of compound one of R^{27} or R^{28} is methyl and the other is hydrogen.

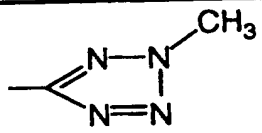
In another preferred group of compounds R is

 or alkoxy 

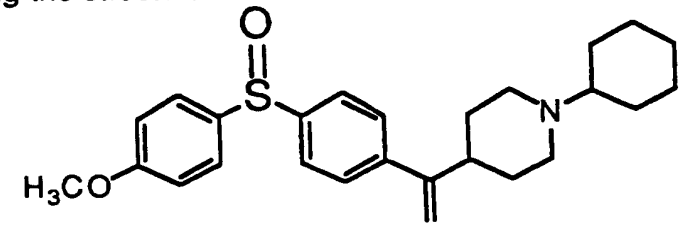
Another preferred group of compounds is the group represented by the formula

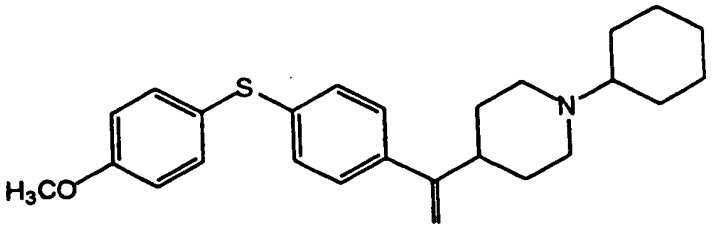


wherein R, X, R^1, R^{27}, and R^{21} are as defined in the following table

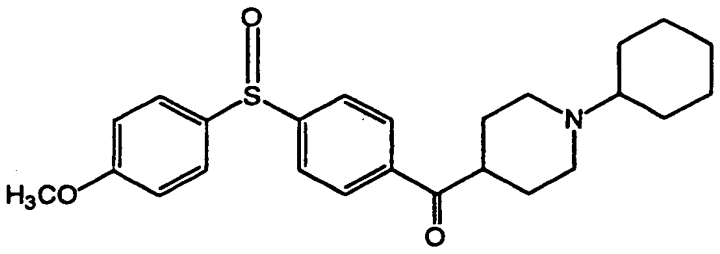
# from table of compounds	R	X	R^1	R^{21}	R^{27}
169	4(CH_3O)-C_6H_4	SO iso A	CN	H	H
227(-)	2-pyrimidinyl	O	cyclohexyl	H	H
289	4(CH_3O)-C_6H_4	SO	CN	CH_3	H
269	2-pyrimidinyl	O	CH_3	H	CH_3
214	4(CH_3O)-C_6H_4	SO 2	CO_2CH_3	H	H
232	2-pyrimidinyl	O	i-propyl	H	H
123	4(CH_3O)-C_6H_4	SO	CH_3	H	H
236	4(CH_3O)-C_6H_4	SO		H	H
296	4-(CH_3O)-C_6H_4	SO	CH_3	CO_2Me	H

or having the structural formula



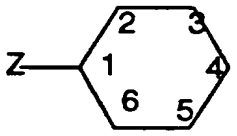


, or



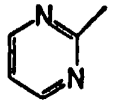
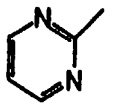
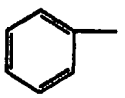
Another group of preferred compounds of formula I are:

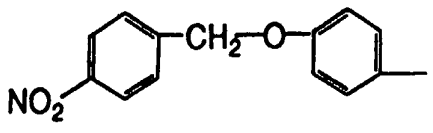
(in the table that follows, when R^2 is substituted cyclohexyl, the substituent positions are numbered as follows:

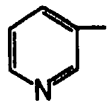
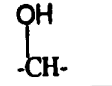


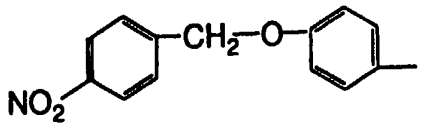
.)

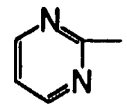
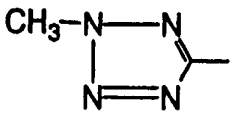
compound #	600	601	602	603	604
R		CH_3	4-(CH_3O)-C_6H_4	4-(CH_3O)-C_6H_4	4(-CH_3O)-C_6H_4
R^1	CH_3	CH_3	CH_3	CH_3	$COOCH_3$
R^2	cyclohexyl (chex)	chex	chex	chex	chex
R^3	H	H	2-Cl	H	H
R^4	H	H	H	H	H
R^{21}	CH_3	H	H	H	H
R^{27}	H	H	H	H	H
R^{28}	H	H	H	H	H
X			SO	SO	SO
Y	N	N	N	CH	N
Z	N	N	N	N	N

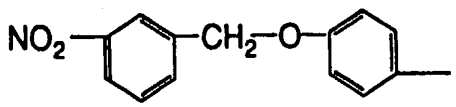
comp. no.	605	606	607	608	609	610	611
R				4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4	*see below	4-(CH_3O) -C_6H_4
R^1	chex	CH_3	CN	CN	CN	CN	CN
R^2	chex	chex	chex	chex	chex	chex	chex
R^3	H	H	H	H	H	H	H
R^4	H	H	H	H	H	H	H
R^{21}	H	H	H	H	CH_3	H	CH_3
R^{27}	H	H	H	H	H	H	H
R^{28}	H	H	H	H	H	H	H
X	S	SO_2	SO	SO_2	SO	S	SO_2
Y	N	N	N	CH	N	N	CH
Z	N	N	N	N	N	N	N

*610. R is 

comp. no.	612	613	614	615	616	617
R		4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4	C_6H_5	* see below
R^1	CH_3	CN	CN	CN	CN	CN
R^2	chex	chex	chex	chex	chex	chex
R^3	H	H	H	H	H	H
R^4	H	H	H	H	H	H
R^{21}	H	H	H	CH_3	H	H
R^{27}	H	(S)-3-CH_3	H	H	H	H
R^{28}	H	H	H	H	H	H
X	SO_2	SO	SO	SO		SO
Y	N	N	CH	N	N	N
Z	N	N	N	N	N	N

* 617. R is 

comp. no.	618	619	620	621	622	623
R	C_6H_5	* see below	2-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4	
R^1	CH_3	CH_3	CN		CN	(R)-CH_3
R^2	chex	chex	chex	chex	chex	chex
R^3	H	H	H	H	H	H
R^4	H	H	H	H	H	H
R^{21}	CH_3	H	H	H	H	H
R^{27}	H	H	H	H	(R)-2-CH_3	2-CH_3
R^{28}	H	H	H	H	H	H
X	O	SO_2	O	SO	SO_2	O
Y	N	N	N	N	N	N
Z	N	N	N	N	N	N

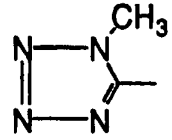
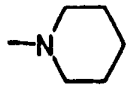


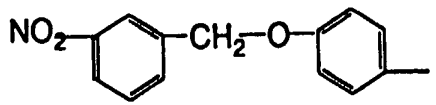
* 619. R is

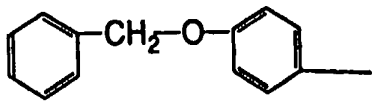
comp. no.	624	625	626	627	628	629
R	* see below	4-(CH_3O)-C_6H_4	* see below	* see below	4-(CH_3O)-C_6H_4	
R^1	CN	-CN	CN	CN	CN	CH_3
R^2	chex		chex	chex	chex	chex
R^3	H	H	H	H	H	H
R^4	H	H	H	H	H	H
R^{21}	H	H	H	H	(R)-2-CH_3	(R)-2-CH_3
R^{27}	H	H	H	H	H	H
R^{28}	H	H	S	SO	SO	O
X	S	S	S	N	N	N
Y	N	N	N	N	N	N
Z	N	CH	N	N	N	N

* 624. R is

626 and 627 R is

comp. no.	630	631	632	633	634	635
R	* see below	* see below	4-(CH_3O) -C_6H_4	4-(CH_3O)- C_6H_4	4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4
R^1	CN	CN	with R^{21} forms = 0	CN	CN	
R^2	chex	chex	chex		chex	chex
R^3	H	H	H	H	H	H
R^4	H	H	H	H	H	H
R^{21}	H	H	-	H	H	H
R^{27}	H	H	H	H	(R)-2-CH_3	H
R^{28}	H	H	H	H	H	H
X	SO	SO	S	SO	S	SO
Y	N	N	CH	N	N	N
Z	N	N	N	CH	N	N

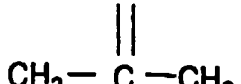
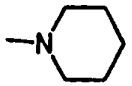
* 630. R is 

*631. R is 

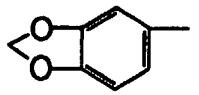
comp. no.	636	637	638	639	640	641
R			4-(CH_3O) -C_6H_4	chex	4-(HO) -C_6H_4	4-(CH_3O) -C_6H_4
R^1	with R^{21} forms = O	CN	with R^{21} forms = 0	CN	CN	with R^{21} forms = N-OCH_3
R^2	chex	chex	chex	chex	chex	chex
R^3	H	H	H	H	H	H
R^4	H	H	H	H	H	H
R^{21}	.	H	.	H	H	.
R^{27}	H	(R)-2-CH_3	H	H	H	H
R^{28}	H	H	H	H	H	H
X	S	SO_2	SO_2	SO_2	S	SO
Y	CH	N	CH	N	N	CH
Z	N	N	N	N	N	N

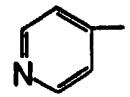
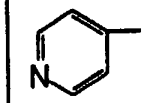
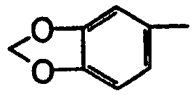
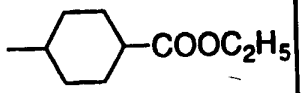
comp. no.	642	643	644	645	646	647
R	C_6H_5	4-(CH_3O)-C_6H_4	4-(CH_3O)-C_6H_4	chex	4-(CH_3O)-C_6H_4	4(-CH_3O)-C_6H_4
R^1	(S)-CH_3	CN	CN	CN	with R^{21} forms = 0	with R^{21} forms = N-OCH_3
R^2	chex	chex	chex	chex	chex	chex
R^3	H	H	H	H	H	H
R^4	H	H	H	H	H	H
R^{21}	H	H	H	H	.	.
R^{27}	(R)-2-CH_3	(S)-2-CH_3	H	H	H	H
R^{28}	H	H	H	H	H	H
X	SO_2	SO_2	C=O	SO	SO	SO
Y	N	N	CH	N	CH	CH
Z	N	N	N	N	N	N

comp. no.	648	649	650	651	652	653
R	C_6H_5	chex	4(-CH_3O)-C_6H_4	C_6H_5	4-(CH_3O)-C_6H_4	4-(CH_3O)-C_6H_4
R^1	(R)-CH_3	CN	CN	with R^{21} forms = O	with R^{21} forms = O	CH_3
R^2	chex	chex	chex	chex	chex	chex
R^3	H	H	H	H	H	H
R^4	H	H	H	H	H	H
R^{21}	H	H	H	-	-	-
R^{27}	(R)-2-CH_3	H	(R)-2-CH_3	H	H	(R)-2-CH_3
R^{28}	H	H	H	H	H	H
X	SO_2	S	SO	S	SO	S
Y	N	N	N	CH	CH	N
Z	N	N	N	N	N	N

comp. no.	654	655	656	657	658	659
R	C_6H_5	4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4	4-(F)-C_6H_4
R^1	with R^{21} forms $=CH_2$	CN	(R)-CH_3	with R^{21} forms 	CN	with R^{21} forms $=CH_2$
R^2	chex	chex	chex	chex		chex
R^3	H	H	H	H	H	H
R^4	H	H	H	H	H	H
R^{21}	-	CH_3	H	-	H	-
R^{27}	H	H	(R)-2-CH_3	H	H	H
R^{28}	H	H	H	H	H	H
X	SO	SO	SO_2	SO	SO	SO
Y	CH	CH	N	CH	N	CH
Z	N	N	N	N	CH	N

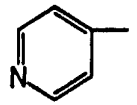
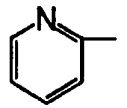
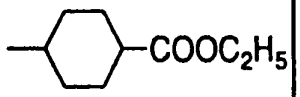
comp. no.	660	661	662	663	664	665
R	C_6H_5	4-(CH_3O)-C_6H_4	4-(F)-C_6H_4	4-(CH_3O)-C_6H_4	4-(CH_3O)-C_6H_4	
R^1	with R^{21} forms =O	$-CONH_2$	with R^{21} forms =O	with R^{21} forms $=CH_2$	$-COOCH_3$	with R^{21} forms = O
R^2	chex	chex	chex	chex		chex
R^3	H	H	H	H	H	H
R^4	H	H	H	H	H	H
R^{21}	-	H	-	-	H	-
R^{27}	H	H	H	H	H	H
R^{28}	H	H	H	H	H	S
X	SO_2	SO	SO_2	SO_2	SO	CH
Y	CH	CH	CH	CH	N	CH
Z	N	N	N	N	CH	N

comp. no.	666	667	668	669	670	671
R	C_6H_5	4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4	4-(F)-C_6H_4	
R^1	with R^{21} forms $=CH_2$	(S)-CH_3	-$COOCH_3$	with R^{21} forms = N-OH	with R^{21} forms = O	with R^{21} forms =O
R^2	chex	chex	chex	chex	chex	chex
R^3	H	H	H	H	H	H
R^4	H	H	H	H	H	H
R^{21}	-	H	H	-	-	-
R^{27}	H	(R)-2-CH_3	H	H	H	H
R^{28}	H	H	H	H	H	H
X	SO_2	SO_2	SO	SO	SO	SO
Y	CH	N	CH	CH	CH	CH
Z	N	N	N	N	N	N

comp. no.	672	673	674	675	676	677
R	4-(CH_3O) -C_6H_4		4-(CH_3O) -C_6H_4		4-(CH_3O) -C_6H_4	
R^1	$-CF_3$	with R^{21} forms = CH_2	see note	with R^{21} forms = CH_2	with R^{21} forms = CH_2	with R^{21} forms = $NOCH_3$ Isomer A
R^2	chex	chex	chex	chex		chex
R^3	H	H	H	H	H	H
R^4	H	H	H	H	H	H
R^{21}	H	-	-	-	-	-
R^{27}	H	H	H	H	H	H
R^{28}	H	H	H	H	H	H
X	SO	S	SO	SO	SO	SO Isomer 1
Y	N	CH	CH	CH	CH	CH
Z	N	N	N	N	N	N

674. R^1 and R^{21} together with the carbon atom to which they are attached form

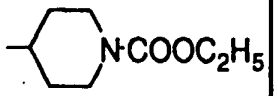
comp. no.	678	679	680	681	682	683
R	4-(CH_3O) -C_6H_4				4-(CH_3O) -C_6H_4	
R^1	F_3C-	with R^{21} forms = O	with R^{21} forms = O	with R^{21} forms = CH_2	with R^{21} forms = CH_2	with R^{21} forms = O
R^2	chex	chex	chex	chex	4(C_6H_5)chex	chex
R^3	H	H	H	H	H	H
R^4	H	H	H	H	H	H
R^{21}	H	-	-	-	-	-
R^{27}	H	H	H	H	H	H
R^{28}	H	H	H	H	H	H
X	SO_2	SO	SO_2	SO_2	SO	S
Y	N	CH	CH	CH	CH	CH
Z	N	N	N	N	N	N

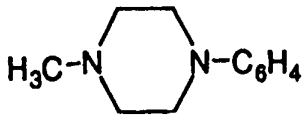
comp. no.	684	685	686	687	688	689
R	4(F)C_6H_4	4-(CH_3O) -C_6H_4		4-(CF_3) -C_6H_4	4-(CH_3O) -C_6H_4	
R^1	with R^{21} forms = CH_2	with R^{21} forms = CH_2	with R^{21} forms = O	with R^{21} forms = CH_2	with R^{21} forms = CH_2	with R^{21} forms = O
R^2	chex		chex	chex	4(C_6H_5)chex	chex
R^3	H	H	H	H	H	H
R^4	H	H	H	H	H	H
R^{21}	-	-	-	-	-	-
R^{27}	H	H	H	H	H	H
R^{28}	H	H	H	H	H	H
X	SO_2	S	SO	SO	SO_2	SO_2
Y	CH	CH	CH	CH	CH	CH
Z	N	N	N	N	N	N

comp. no.	690	691	692	693	694	695
R		4-(CH_3O) -C_6H_4		3-(CH_3O) -C_6H_4	2-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_5
R^1	with R^{21} forms = CH_2	-CN	with R^{21} forms = CH_2	with R^{21} forms = O	with R^{21} forms = O	$-CH_3$
R^2	chex	chex	chex	chex	chex	chex
R^3	H	H	H	H	H	H
R^4	H	H	H	H	H	H
R^{21}	.	H	.	.	.	$-CH_3$
R^{27}	H	H	H	H	H	H
R^{28}	H	H	H	H	H	H
X	S	SO	SO	SO_2	SO_2	SO_2
Y	CH	CH	CH	CH	CH	CH
Z	N	N	N	N	N	N

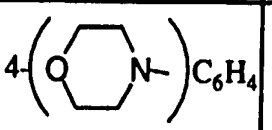
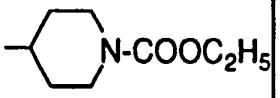
comp. no.	696	697	698	699	700	701
R	2-(CH_3O) -C_6H_4		4-benzyloxy phenyl	2-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4
R^1	with R^{21} forms = CH_2	with R^{21} forms = O	with R^{21} forms = CH_2	with R^{21} forms = O	with R^{21} forms = O	with R^{21} forms = O
R^2	chex	chex	chex	chex	chex	chex
R^3	H	H	H	H	H	H
R^4	H	H	H	H	H	H
R^{21}	-	-	-	-	-	-
R^{27}	H	H	H	H	2-(CH_3)	H
R^{28}	H	H	H	H	H	H
X	O	SO	SO_2	S	SO_2	SO_2-NH
Y	CH	CH	CH	CH	CH	CH
Z	N	N	N	N	N	N

comp. no.	702	703	704	705	706	707
R	4-(CH_3O) -C_6H_5		3-(CH_3O) -C_6H_5	4-(CH_3O) -C_6H_5	4-(CH_3O) -C_6H_5	4-(CH_3O) -C_6H_5
R^1	-CN	with R^{21} forms = CH_2	with R^{21} forms = O	$-CH_3$	with R^{21} forms = CH_2	(S)-C_2H_5
R^2	chex	chex	chex	chex	chex	chex
R^3	H	H	H	H	H	H
R^4	H	H	H	H	H	H
R^{21}	H	-	-	$-CH_3$	-	(R)-2-(CH_3)
R^{27}	H	H	H	H	2(CH_3)	H
R^{28}	H	H	H	H	H	H
X	SO	SO_2	SO	SO	SO_2	SO_2
Y	CH	CH	CH	CH	CH	CH
Z	N	N	N	N	N	N

comp. no.	708	709	710	711	712	713
R	4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_5	3-(Cl)-C_6H_4	4(-CH_3O) -C_6H_4	see note 712.	4-(CH_3O) -C_6H_4
R^1	(R)-C_2H_5	with R^{21} forms = O	CH_3	with R^{21} forms = CH_2	with R^{21} forms = O	-CN
R^2	chex	chex			chex	chex
R^3	H	H	H	H	H	H
R^4	H	H	H	H	H	H
R^{21}	H	-	H	-	-	-CH_3
R^{27}	(R)-2-(CH_3)	H	H	H	H	H
R^{28}	H	H	H	H	H	H
X	SO_2	SO_2	SO_2	SO_2	SO_2	SO_2
Y	N	CH	N	CH	CH	CH
Z	N	N	N	N	N	N

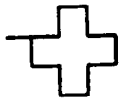
712. R is 

comp. no.	714	715	716	717	718	719
R	4-CH_3O)-C_6H_4	4-(CH_3O)-C_6H_4	4-(HO)-C_6H_4	4-(CH_3O)-C_6H_4	4(-CH_3O)-C_6H_4	4-(CH_3O)-C_6H_4
R^1	(S)-2-propyl	-CH_3 isomer 1	with R^{21} forms = O	with R^{21} forms = CH_2	with R^{21} forms = O	with R^{21} forms = O
R^2	chex	chex	chex		chex	
R^3	H	H	H	H	H	H
R^4	H	H	H	H	H	H
R^{21}	H	H	.	.	.	.
R^{27}	(R)-2(CH_3)	(R)-2-n-C_3H_7	H	H	H	H
R^{28}	H	H	H	H	H	H
X	SO_2	SO_2	SO_2	SO_2	-CONH-	SO_2
Y	N	N	CH	CH	CH	CH
Z	N	N	N	N	N	N

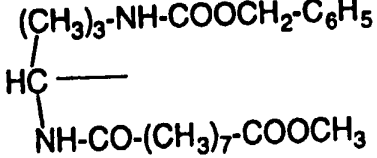
comp. no.	720	721	722	723	724	725
R	4-(CH_3O)-C_6H_4	4-(CH_3O) -C_6H_4	4-(CF_3O) -C_6H_4		4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4
R^1	(R)-2-propyl	CH_3 isomer 2	with R^{21} forms = O	with R^{21} forms = O	-CH_3	with R^{21} forms = O
R^2	chex	chex	chex	chex	chex	
R^3	H	H	H	H	H	H
R^4	H	H	H	H	H	H
R^{21}	H	H	-	-	-CN	-
R^{27}	(R)-2(CH_3)	(R)-2-n-propyl	H	H	H	H
R^{28}	H	H	H	H	H	H
X	SO_2	SO_2	SO_2	SO_2	SO_2	SO
Y	N	N	CH	CH	CH	CH
Z	N	N	N	N	N	N

comp. no.	726	727	728	729	730	731
R	4-(CH_3O)-C_6H_4	4-(CH_3O)-C_6H_4	4-(CH_3O)-C_6H_4	4-(CH_3O)-C_6H_4	4-(CH_3O)-C_6H_4	4-(CH_3O)-C_6H_4
R^1	(S)-CH_3	(S)-CH_3	(S)-CH_3	CH_3	with R^{21} forms = O	(S)-CH_3
R^2	cyclopentyl	cycloheptyl	cyclobutyl		chex	cyclopropyl
R^3	H	H	H	H	H	H
R^4	H	H	H	H	H	H
R^{21}	H	H	H	H	-	H
R^{27}	(R)-2-(CH_3)	3-(CH_3)	(R)-2-(CH_3)	H	(R)-2-(CH_3)	(R)-2-(CH_3)
R^{28}	H	H	H	H	H	H
X	SO_2	SO_2	SO_2	SO	SO_2	SO_2
Y	N	N	N	N	N	N
Z	N	N	N	CH	N	N

comp. no.	732	733	734	735	736	737
R	4-(CH_3O)-C_6H_4	4-(CH_3O)-C_6H_4	4-(CH_3O)-C_6H_4	4-(CH_3O)-C_6H_4	4-(CH_3O)-C_6H_4	4-(CH_3O)-C_6H_4
R^1	(S)-CH_3	(S)-CH_3	(S)-CH_3	CH_3	(S)-CH_3	(S)-CH_3
R^2	cyclopentyl	cyclooctyl	cyclobutyl			cyclopropyl
R^3	H	H	H	H	H	H
R^4	H	H	H	H	H	H
R^{21}	H	H	H	H	H	H
R^{27}	3(CH_3)	(R)-2(CH_3)	3(CH_3)	H	(R)-2(CH_3)	3(CH_3)
R^{28}	H	H	H	H	H	H
X	SO_2	SO_2	SO_2	SO_2	SO_2	SO_2
Y	N	N	N	N	N	N
Z	N	N	N	CH	N	N

comp. no.	738	739	740	741	742	743
R	4-(CH_3O)-C_6H_4	4-(CH_3O)-C_6H_4	4-(CH_3O)-C_6H_4	4-(CH_3O)-C_6H_4	44-(CH_3O)-C_6H_4	See note 743
R^1	(S)-CH_3	(S)-CH_3	with R^{21} forms = CH_2	(S)-CH_3	(S)-CH_3	CH_3
R^2	cycloheptyl	cyclooctyl	chex	chex		chex
R^3	H	H	H	H	H	H
R^4	H	H	H	H	H	H
R^{21}	H	H	-	H	H	H
R^{27}	(R)-2(CH_3)	3(CH_3)	with R^{28} forms 3,5-$(CH_2)_2$-	3-(CH_3)	3-(CH_3)	H
R^{28}	H	H	-	H	H	H
X	SO_2	SO_2	SO_2	SO_2	SO_2	-CONH-
Y	N	N	CH	N	N	N
Z	N	N	N	N	N	N

743. R is



comp. no.	744	745	746	747	748	749
R	See Note	See Note	See Note	See Note	4(-CH_3O) -C_6H_4	See Note
R^1	CH_3	CH_3	CN	CH_3	-OH	CH_3
R^2	chex	chex	chex	chex	chex	chex
R^3	H	H	H	H	H	H
R^4	H	H	H	H	H	H
R^{21}	H	H	H	H	H	H
R^{27}	H	H	H	H	H	H
R^{28}	H	H	H	H	H	H
X	-CONH-	-CONH-	S	O	SO	-CONH-
Y	N	N	N	N	CH	N
Z	N	N	N	N	N	N

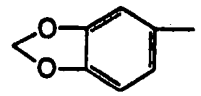
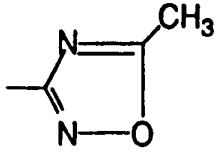
745. R is

747. R is

744. R is

746. R. is 4-[CH_3-N(CH_3)-COO]-C_6H_4

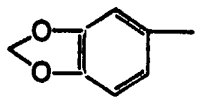
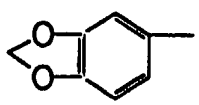
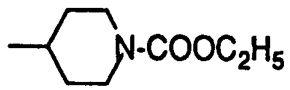
749. R is

comp. no.	750	751	752	753	754	755
R	See Note	See Note	See Note	4-(CH_3O)-C_6H_4		4-(CH_3O)-C_6H_4
R^1	CH_3	CH_3	CN		with R^{21} forms =O	with R^{21} forms =O
R^2	chex	chex	chex	chex	chex	chex
R^3	H	H	H	H	H	H
R^4	H	H	H	H	H	H
R^{21}	H	H	H	H	-	-
R^{27}	H	H	H	H	H	1-(CH_3)
R^{28}	H	H	H	H	H	H
X	-CONH-	-CONH-	SO_2	SO	SO	SO
Y	N	N	N	N	CH	CH
Z	N	N	N	N	N	N

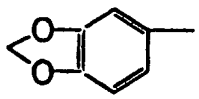
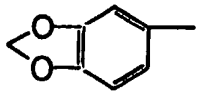
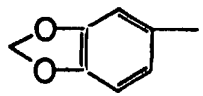
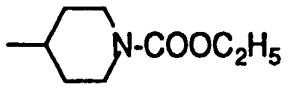
751. R is

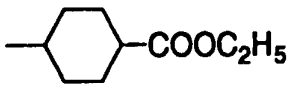
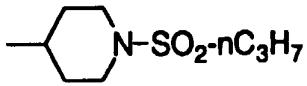
750 R is

752. R is4-[(CH3)2N-COO]-C6H4-

comp. no.	756	757	758	759	760	761
R	4-(CH_3O) -C_6H_4		4-(CH_3O) -C_6H_4		4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4
R^1	OH	with R^{21} forms = O	-CH_3OH	OH	with R^{21} forms = CH_2	OH
R^2	chex	chex	chex	chex		chex
R^3	H	H	H	H	H	H
R^4	H	H	H	H	H	H
R^{21}	2-propyl	-	H	CH_3	-	ethyl
R^{27}	H	H	H	H	H	H
R^{28}	H	H	H	H	H	H
X	SO	SO	S	SO	SO_2	SO
Y	CH	CH	CH	CH	CH	CH
Z	N	N	N	N	N	N

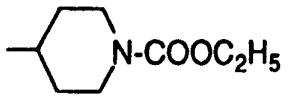
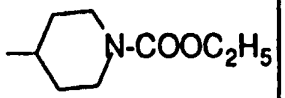
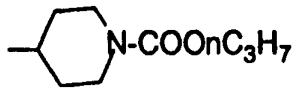
comp. no.	762	763	764	765	766	767
R		4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4
R^1	with R^{21} forms =CH_2	with R^{21} forms = CH_2		with R^{21} forms = CH_2	-CH_2-OH	-CH_2-OH
R^2	chex		chex		chex	chex
R^3	H	H	H	H	H	H
R^4	H	H	H	H	H	H
R^{21}	.	.	H	.	H	H
R^{27}	H	H	H	H	H	H
R^{28}	H	H	H	H	H	H
X	SO	SO	S	S	SO_2	SO
Y	CH	CH	CH	CH	CH	CH
Z	N	N	N	N	N	N

comp. no.	768	769	770	771	772	773
R		4-(CH_3O)-C_6H_4	4-(CH_3O)-C_6H_4	4-(CH_3O)-C_6H_4		
R^1	with R^{21} forms = N-OCH_3 Isomer B	-CH_2-OCO-CH_3	with R^{21} forms = CF_2	CH_3	with R^{21} forms =N-OCH_3 Isomer A	with R^{21} forms = N-OCH_3 Isomer B
R^2	chex	chex	chex		chex	chex
R^3	H	H	H	H	H	H
R^4	H	H	H	H	H	H
R^{21}	-	H	-	H	-	-
R^{27}	H	H	H	H	H	H
R^{28}	H	H	H	H	H	H
X	SO Isomer 2	SO	SO_2	SO_2	SO Isomer 2	SO Isomer 1
Y	CH	CH	CH	CH	CH	CH
Z	N	N	N	N	N	N

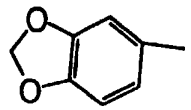
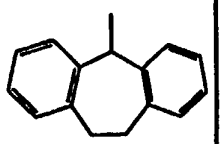
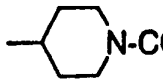
comp. no.	774	775	776	777	778
R	4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4	omit
R^1	CH_3-O-CO-CH_3	with R^{21} forms = CF_2	with R^{21} forms = CH_2	CH_3	
R^2	chex	chex			
R^3	H	H	H	H	
R^4	H	H	H	H	
R^{21}	H	-	-	H	
R^{27}	H	H	H	(R)-2(CH_3)	
R^{28}	H	H	H	H	
X	SO_2	SO	SO_2	SO_2	
Y	CH	CH	CH	CH	
Z	N	N	N	N	

comp. no.	779	780	781	782	783
R	4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4
R^1	n-butyl isomer 1	(CH_3)2-C_6H_4 isomer 1	with R^{21} forms =CH_2	with R^{21} forms =CH_2	(S)-CH_3
R^2	chex	chex			
R^3	H	H	H	H	H
R^4	H	H	H	H	H
R^{21}	H	H	.	.	H
R^{27}	(R)-2-(CH_3)	(R)-2-CH_3	H	H	(R)-2-CH_3
R^{28}	H	H	H	H	H
X	SO_2	SO_2	SO_2	S	SO_2
Y	N	N	CH	CH	N
Z	N	N	N	N	N

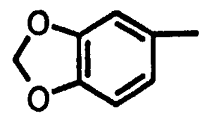
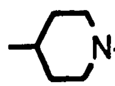
comp. no.	784	785	786	787	788
R	4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4
R^1	n-butyl isomer 2	-$(CH_2)_3$ -C_6H_5 isomer 2	cyclopentyl isomer 1	with R^{21} forms =CH_2	(S)-CH_3
R^2	chex	chex	chex		
R^3	H	H	H	H	H
R^4	H	H	H	H	H
R^{21}	H	H	H	-	H
R^{27}	(R)-2-CH_3	(R)-2-CH_3	(R)-2-CH_3	H	(R)-2-CH_3
R^{28}	H	H	H	H	H
X	SO_2	SO_2	SO_2	SO	SO_2
Y	N	N	N	CH	N
Z	N	N	N	N	N

comp. no.	789	790	791	792	793
R	4-(CH_3O)-C_6H_4	4-(CH_3O)-C_6H_4	4-(CH_3O)-C_6H_4	(see note 792)-	4-(CH_3O)-C_6H_4
R^1	(S)-CH_3	(R)-2-CH_3	(S)-CH_3	CN	(S)-CH_3
R^2				chex	H
R^3	H	H	H	H	H
R^4	H	H	H	H	H
R^{21}	H	H	H	H	H
R^{27}	(R)-2-(CH_3)	(R)-2-CH_3	(R)-2-CH_3	H	(R)-2-CH_3
R^{28}	H	H	H	H	H
X	S	S	SO_2	SO	SO_2
Y	N	N	N	N	N
Z	N	N	N	N	N

792. R is 4-[$(CH_3)_2NCOO$]-C_6H_4-

comp. no.	794	795	796	797	798
R	4-(CH_3O)-C_6H_4		4-(CH_3O)-C_6H_4	4-(CH_3O)-C_6H_4	4-(CH_3O)-C_6H_4
R^1	(S)-CH_3	(R)-CH_3	(S)-CH_3	(S)-CH_3	CH_3
R^2		chex	 N-COO-t-butyl	 N-CONHC_2H_5	1-CH_3-chex
R^3	H	H	H	H	H
R^4	H	H	H	H	H
R^{21}	H	H	H	H	H
R^{27}	(R)-2-(CH_3)	(R)-2-(CH_3)	(R)-2-(CH_3)	(R)-2-CH_3	H
R^{28}	H	H	H	H	H
X	SO_2	SO_2	S	SO_2	SO_2
Y	N	N	N	N	N
Z	N	N	N	N	N

comp. no.	799	800	801	802	803
R	4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4		4-(CH_3O) -C_6H_4	4-(CH_3O) -C_6H_4
R^1	(R)-CH_3	CH_3	(S)-CH_3	CH_3	(S)-CH_3
R^2		chex	chex	chex	4-(OH)-chex
R^3	H	H	H	H	H
R^4	H	H	H	H	H
R^{21}	H	CH_3	H	CH_3	H
R^{27}	(R)-2-CH_3	2-CH_3	(R)-2-CH_3	2-CH_3	3-CH_3
R^{28}	H	H	H	H	H
X	SO_2	SO_2	SO_2	S	SO_2
Y	N	CH	N	CH	N
Z	N	N	N	N	N

comp. no.	804	805
R	4-(CH_3O) -C_6H_4	
R^1	(S)-CH_3	(S)-CH_3
R^2	trans 4-(OH)-chex	 N-SO_2-n-C_3H_7
R^3	H	H
R^4	H	H
R^{21}	H	H
R^{27}	(R)-2-(CH_3)	(R)-2-CH_3
R^{28}	H	H
X	SO_2	SO_2
Y	N	N
Z	N	N

Another aspect of the invention is a pharmaceutical composition which comprises a compound having structural formula I as defined above in combination with a pharmaceutically acceptable carrier.

Another aspect of the invention is the use of a compound formula I for the preparation of a pharmaceutical composition useful in the treatment of cognitive disorders and neurodegenerative diseases such as Alzheimer's disease.

Yet another aspect of the invention comprises a method for making a pharmaceutical composition comprising mixing a compound of formula I with a pharmaceutically acceptable carrier.

Another aspect of this invention is a method for treating a cognitive or neurodegenerative disease comprising administering to a patient suffering from said disease an effective amount of a compound of formula I.

Another aspect of this invention is a method for treating cognitive and neurodegenerative diseases, such as Alzheimer's disease with a compound of formula I in combination with an acetylcholinesterase inhibitor.

Another aspect of this invention is a method for treating a cognitive or neurodegenerative disease comprising administering to a patient suffering from said disease an effective amount of a combination of a compound capable of enhancing acetylcholine release (preferably an m2 or m4 selective muscarinic antagonist) with an acetycholinesterase inhibitor.

Another aspect of this invention is a kit comprising in separate containers in a single package pharmaceutical compounds for use in combination to treat cognitive disorders in one container a compound of formula I or a compound capable of enhancing acetylcholine release (preferably an m2 or m4 selective muscarinic antagonist) in a pharmaceutically acceptable carrier and in a

second container an acetylcholinesterase inhibitor in a pharmaceutically acceptable carrier, the combined quantities being an effective amount.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates the dose related effects of i.p. administration of a compound of this invention on acetylcholine (ACh) release from cortex of conscious rat.

Figure 2 is a plot similar to figure 1 for ACh release from the striatum following i.p. administration .

Figure 3 illustrates the effect of 3 mg/kg of Tacrine (i.p. administration) on ACh release from striatum of conscious rat.

Figure 4 is a plot similar to figure 4 for 1 mg/kg of a compound of this invention (i.p. administration).

Figure 5 is a plot similar to figure 4 for 1 mg/kg of a compound of this invention in combination with 3 mg/kg of Tacrine (both i.p. administration).

DETAILED DESCRIPTION

Except where stated otherwise the following definitions apply throughout the present specification and claims. These definitions apply regardless of whether a term is used by itself or in combination with other terms. Hence the definition of "alkyl" applies to "alkyl" as well as the "alkyl" portions of "alkoxy", "haloalkyl", etc.

Alkyl represents a straight or branched saturated hydrocarbon chain having 1 to 20 carbon atoms, more preferably 1 to 8 carbon atoms.

Alkenyl represents a straight or branched hydrocarbon chain of from 2 to 15 carbon atoms, more preferably 2 to 12 carbon atoms, having at least one carbon-to-carbon double bond.

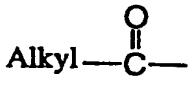
Alkynyl represents a straight or branched hydrocarbon chain of from 2 to 10 carbon atoms, more preferably 2 to 8 carbon atoms, having at least one carbon-to-carbon triple bond.

Cycloalkyl represents a saturated carbocyclic ring having 3 to 12 carbon atoms.

Cycloalkenyl represents a carbocyclic ring having from 5 to 8 carbon atoms and at least one carbon-to-carbon double bond in the ring.

Bicycloalkyl represents a saturated bridged carbocyclic ring having 5 to 12 carbon atoms.

Acyl represents a radical of the formula

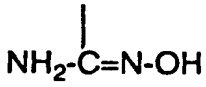
 wherein alkyl is as defined previously.

Halo represents fluoro, chloro, bromo or iodo.

Aryl represents phenyl or naphthyl.

Polyhalo represent substitution of at least 2 halo atoms to the group modified by the term "polyhalo".

Hydroxyguanidino represents a group having the formula



Azabicyclo represents a saturated bridged ring containing from 4 to 8 carbon atoms and at least one nitrogen atom.

Sulfonyl represents a group of the formula $-SO_2-$.

Sulfinyl represents a group of the formula -SO-.

Alkylene represents a group having the formula $-(CH_2)_q$, wherein q is an integer of from 1 to 20.

Naturally occurring amino acid (NOAA) means an acid selected from the group consisting of alanine(ala), arginine (arg), asparagine (asn), aspartic acid (asp), cysteine (cys), glutamine (gln), glutamic acid (glu), glycine (gly),

histadine (his), isoleucine (ile), leucine (leu), lysine (lys), methionine (met), phenylalanine (phe), proline (pro), serine (ser), threonine (thr), tryptophan (trp), tyrosine (tyr), and valine (val).

Nitrogen protecting group (Prot) means a group capable of protecting a nitrogen on a naturally occurring amino acid (or an enantiomer thereof) from reaction. Preferred nitrogen protecting groups are carbobenzyloxy (CBZ), $CH_3OCO(CH_2)_9CO$, and t-butoxycarbonyl. Of course any operable nitrogen protecting group is included.

When a variable appears more than once in the structural formula, for example R^5 when X is $-C(OR^5)_2-$, the identity of each variable appearing more than once may be independently selected from the definition for that variable.

Compounds of this invention may exist in at least two stereo configurations based on the asymmetric carbon to which R^1 is attached, provided that R^1 and R^{21} are not identical. Further stereoisomerism is present when X is SO, or $C(OR^5)_2$ (when the two R^5 groups are not the same) or when R is $-CR^5=C=CR^6$, . Also within formula I there are numerous other possibilities for stereoisomerism. All possible stereoisomers of formula I are within the scope of the invention.

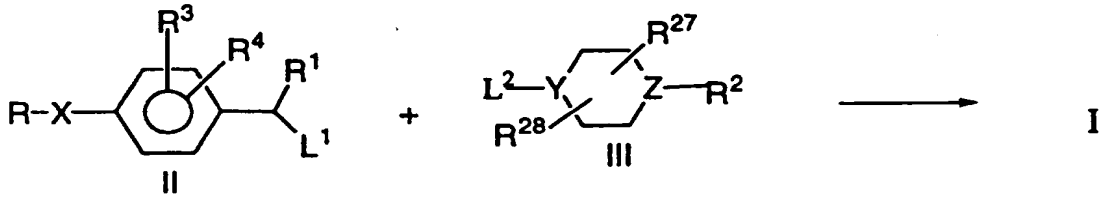
Compound of formula I can exist in unsolvated as well as solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like, are equivalent to the unsolvated forms for purposes of this invention.

A compound of formula I may form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those skilled in the art. The salts are prepared by contacting the free base forms with a sufficient amount of the desired acid to produce a salt in

the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia or sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the salts are otherwise equivalent to their respective free base forms for purposes of the invention.

Compound in accordance with formula I may be produced by processes known to those skilled in the art as shown by the following reaction steps:

Process A (for compounds of formula I where R^{21} is H and X is O, SO, or SO_2)

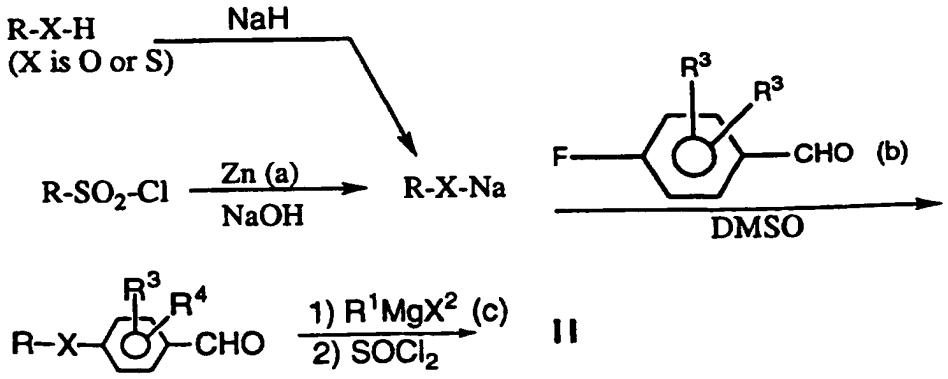


II III I

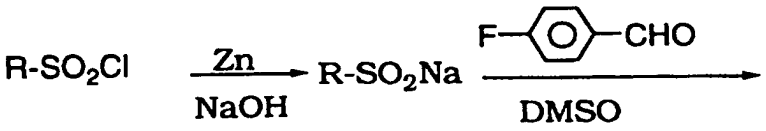
wherein L^1 is a leaving group and L^2 is H or an alkali metal and Y, Z, R, R^1, R^2, R^3, R^4, R^{27} and R^{28} are as defined above for formula I, and X is O, SO or SO_2.

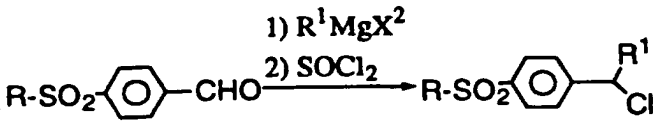
Process A is preferably carried out neat or in a solvent such as DMF, DMSO, or acetonitrile, at temperatures ranging from 0°C to 110°C for a period of about 1-24 hours. It is preferable that L^1 be a chloride leaving group, but other leaving groups such as bromide, or mesylate, will suffice. It is preferable that L^2 be hydrogen.

Starting materials of formula II when X is O, SO, or SO_2 may be formed by the following reaction sequence

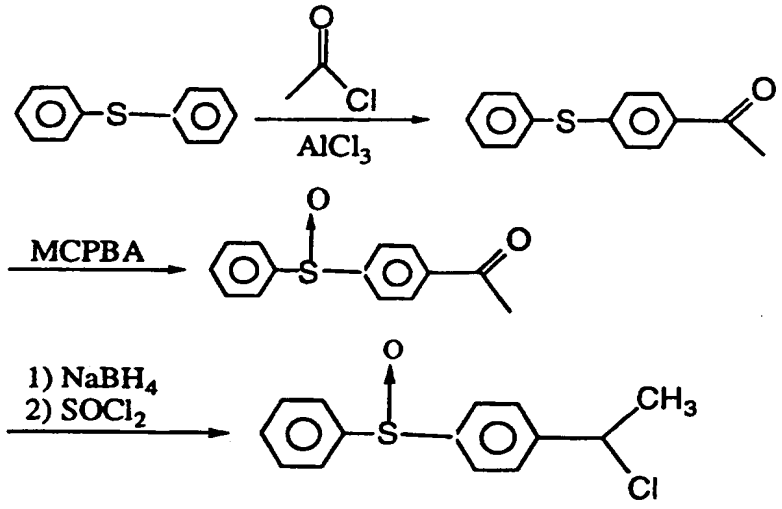


In step (a) the chloride compound is reacted with sodium hydroxide in presence of zinc in solvent such as water, at 50-95°C for 1-3 hours. Alternatively R-X-H is reacted with NaH in solvent such as THF or DMF at 0° to room temperature for 1-3 hours. In step (b) the substituted benzaldehyde is added to the reaction mixture from step (a) and the reaction carried out for 1-24 hours at 20-70°C. In step (c) X^2 represents e.g. chloride or bromide. The reaction with R^1MgX^2 is carried out in THF or diethyl ether solvent at 0°C -70°C for 1-24 hours. Reaction with $SOCl_2$ is preferably done in excess thionyl chloride as solvent at 25-70°C for 1-24 hours. Compounds of formula III are readily available. Some reaction schemes for making other compounds of formula II are shown below:

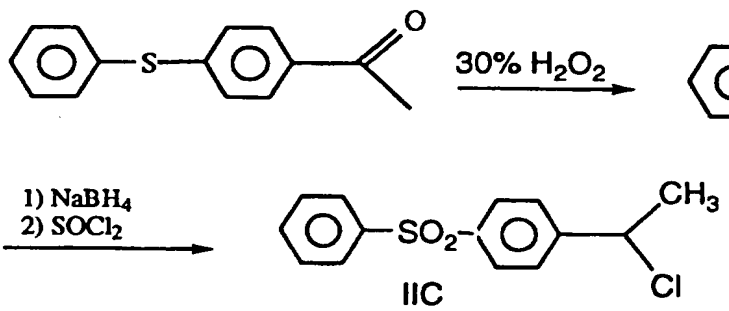




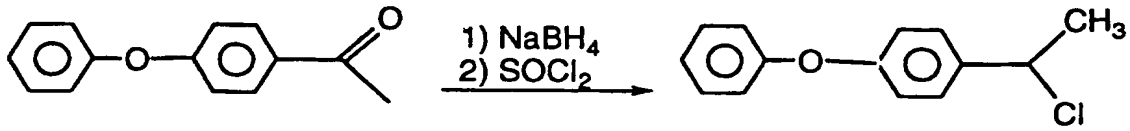
IIA



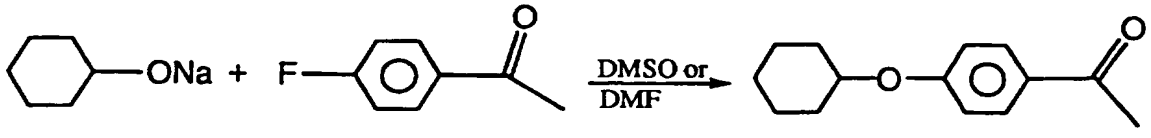
IIB



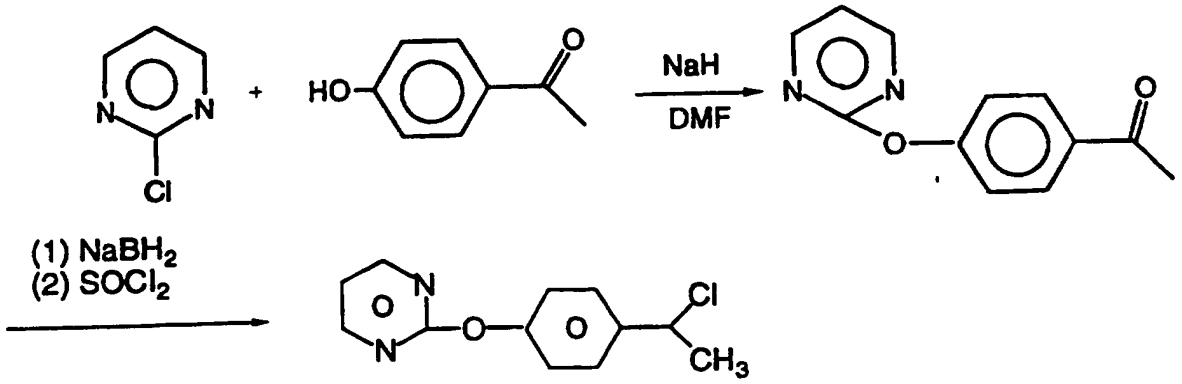
IIC



IID

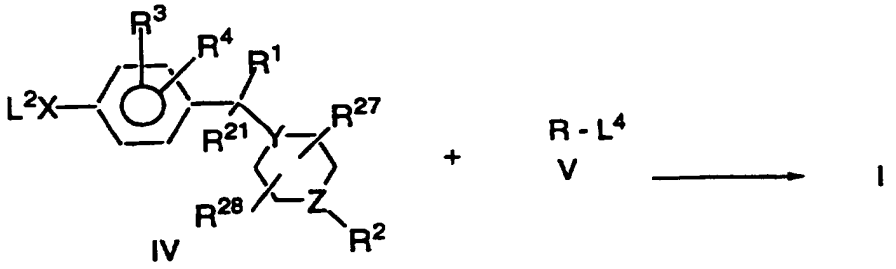


IIE



IIF

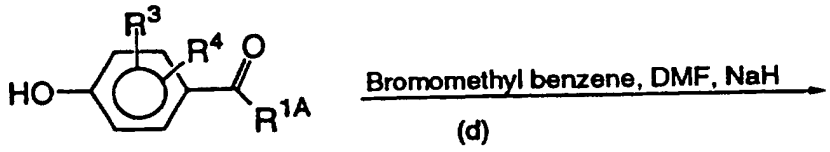
Process B

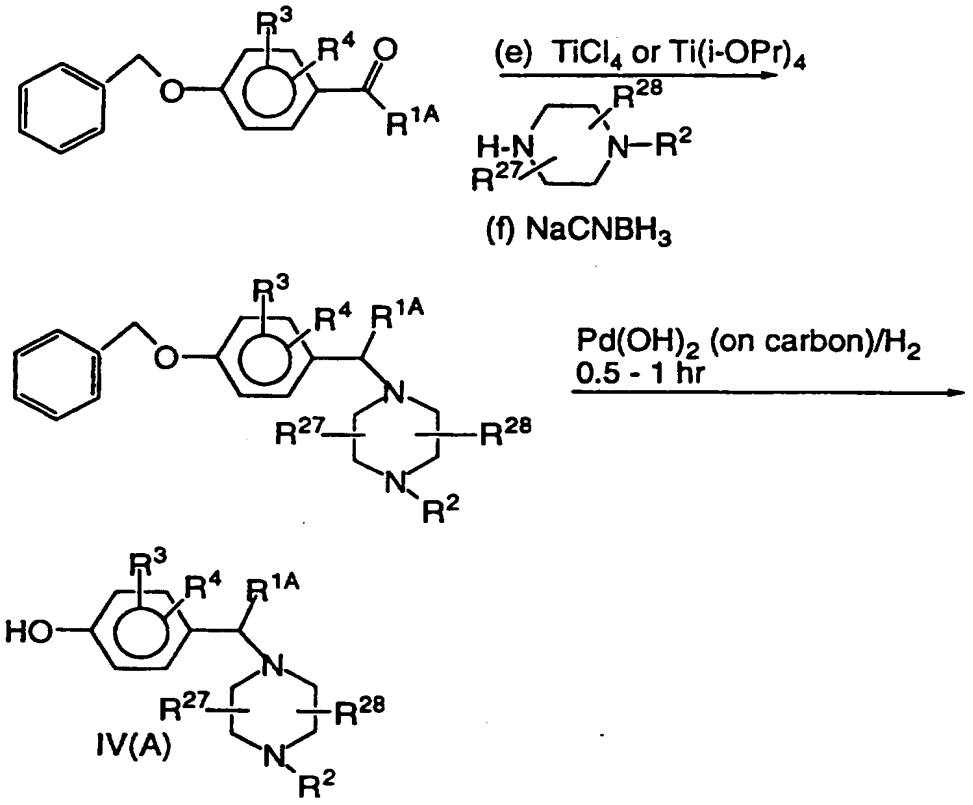


wherein L^4 is a leaving group and L^2 is H or alkali metal and X, Y, Z, R, R^1, R^2, R^3, R^4, R^{21}, R^{27} and R^{28} are as defined above for formula I.

Process B is preferably carried out in solvent such as DMF at about 25 to 120°C for about 1-24 hours. It is preferred that L^2 be Na or hydrogen and that L^4 be a chloride leaving group.

Compounds of formula IV may be produced by the following reaction scheme:





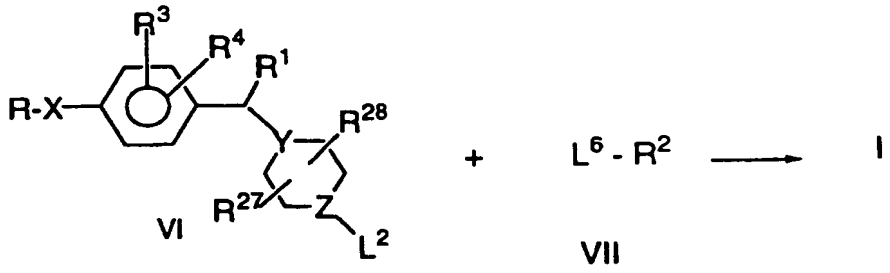
In the above reactions scheme R^{1A} is preferably in accordance with the definition of R^7 for formula I.

Step (d) may be perfomed in acetone or DMF solvent at 20-100°C, for 1-24 hours under basic conditions, e.g. with K_2CO_3.

Step (e) may be performed neat or in methylene chloride, at 20-70°C, for 1-24 hours.

Step (f) may be performed in ethanol or methanol at 25-70°C for 1-24 hours.

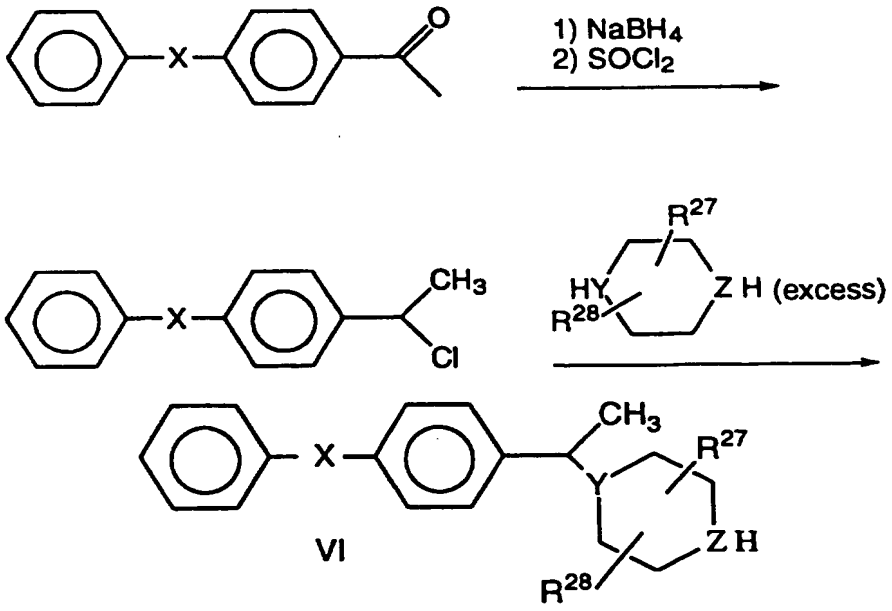
Process C (for compounds of formula I where R^{21} is H)



wherein L^6 is a leaving group and L^2 is H or alkali metal and X, Y, Z, R, R^1, R^2, R^3, R^4, R^{27} and R^{28} are as defined above for formula I.

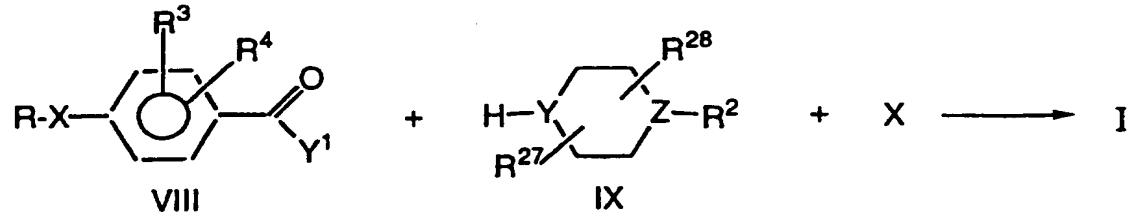
Process C is preferably carried out in solvent such as DMF, DMSO or acetonitrile at about 0 to 110°C for 1-24 hours. It is preferable that L^2 be hydrogen and that L^6 be a chloride leaving group.

Compounds of formula VI may be produced by the following reaction scheme:



Other compounds of formula VI may be produced by similar reactions.

Process D (for compounds of formula I where R^{21} is H)

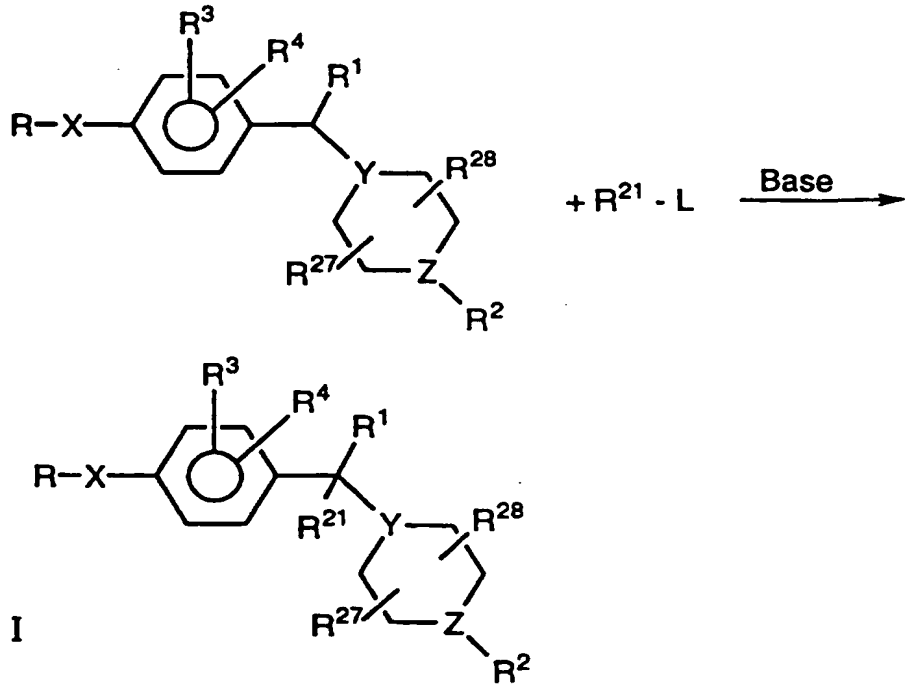


VIII IX

werein Y^1 is H or alkyl, and compound X is $(alkyl)_2AlCN$ or a Grignard reagent.

Process D is preferably carried out by first treating a compound of formula VIII, titanium tetrachloride ($TiCl_4$) or titanium tetra isopropoxide, and a compound of formula IX neat or in solvent such as methylene chloride for about 1-24 hours at 20 to 70°C. Finally a compound of formula X is added and the mixture is stirred for 1-24 hours at 20-70°C. Compounds of formula VIII may be produced by steps (a) and (b) of process A.

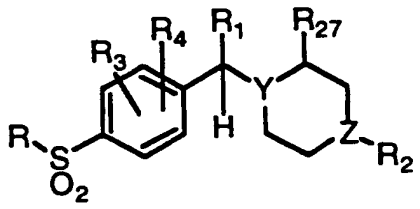
Process E (for compounds wherein R^{21} is not H)



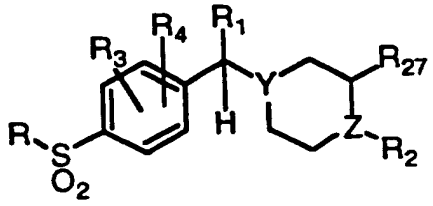
I

In the above reaction L is a leaving group. the reaction is performed insolvent, e.g. THF, at -70 C to room temperature for 1/2 to 12 hours.

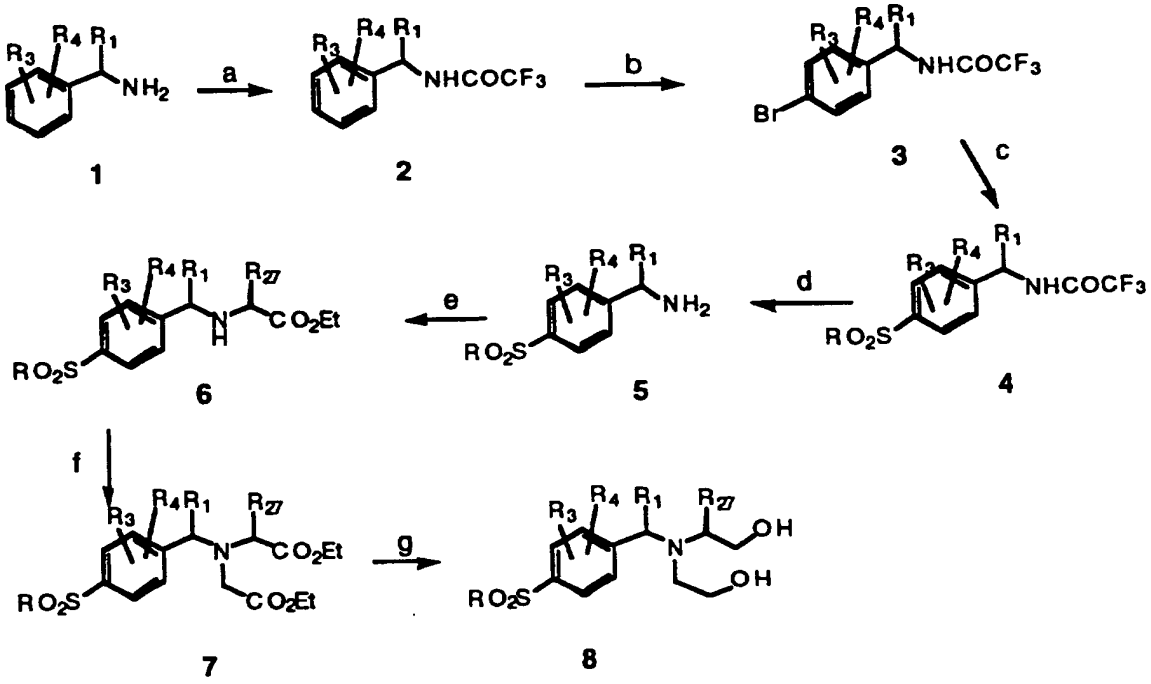
Process F (for compounds of structure XI or XII when Y and Z are both N, especially for non-racemic compounds where R^1 and R^{27} are both CH_3)



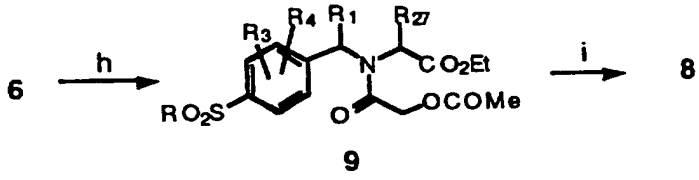
XI



XII

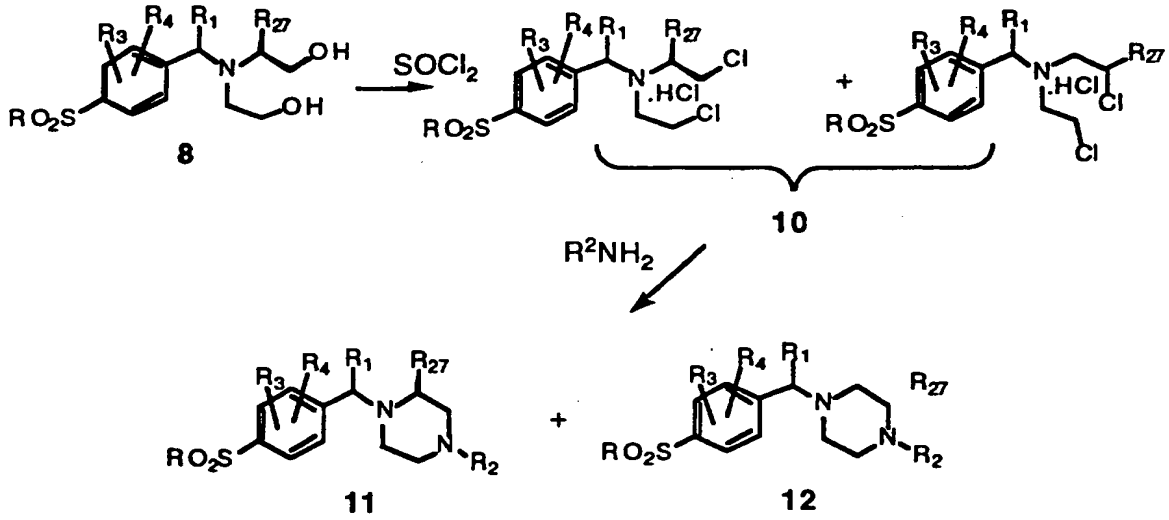


Alternative to steps (f) and (g):



Reagents: **a:** $(CF_3CO)_2O$; **b:** dibromodimethylhydantoin, CH_3SO_3H; **c:** MeLi, then n-BuLi, then RSO_2F; **d:** NaOH; **e:** $R_{27}CH(OSO_2CF_3)CO_2Et$, K_2CO_3; **f:** ICH_2CO_2Et, Na_2CO_3; **g:** $LiAlH_4$; **h:** $AcOCH_2COCl$; **i:** $BH_3.Me_2S$.

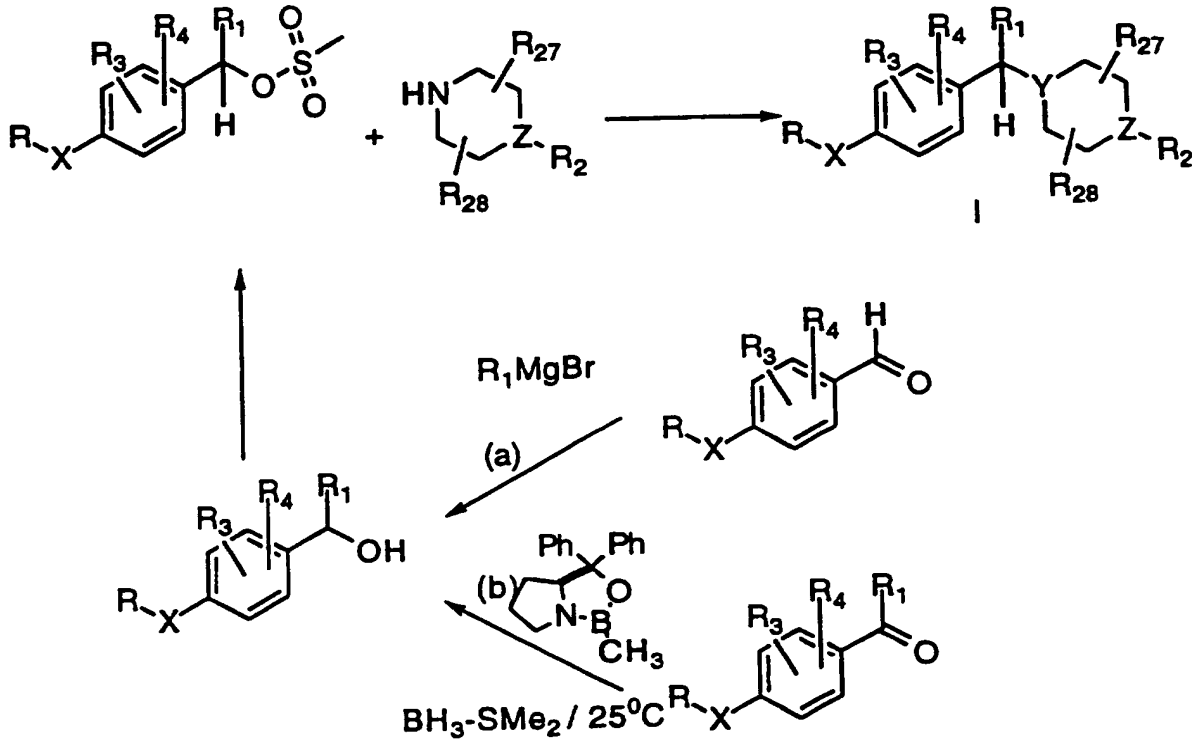
Reaction of diol (**8**) with thionyl chloride gives a mixture of chlorides (**10**), which are in equilibrium with each other. This mixture is reacted with primary amines to afford compounds of the invention (**11**) and (**12**).



When the starting material **1** and reagent $R_{27}CH(OSO_2CF_3)CO_2Et$ are optically pure or enriched, the products **11** and **12** are non-racemic.

Process G

For compounds of formula I where R^1 is alkyl, R^{21} is H, and Y is N, especially compounds of this type when X is SO_2 and the carbon to which R^1 and R^{21} are attached is not racemic.



The above reactions may be followed if necessary or desired by one or more of the following steps; (a) removing any protective groups from the compound so produced; (b) converting the compound so-produced to a pharmaceutically acceptable salt, ester and/or solvate; (c) converting a compound in accordance with formula I so produced to another compound in accordance with formula I, and (d) isolating a compound of formula I, including separating stereoisomers of formula I.

Based on the foregoing reaction sequence, those skilled in the art will be able to select starting materials needed to produce any compound in accordance with formula I.

In the above processes it is sometimes desirable and/or necessary to protect certain groups during the reactions. Conventional protecting groups, familiar to those skilled in the art, are operable. After the reaction or reactions, the protecting groups may be removed by standard procedures.

The compounds of formula I exhibit selective m2 and/or m4 muscarinic antagonizing activity, which has been correlated with pharmaceutical activity for treating cognitive disorders such as Alzheimers disease and senile dementia.

The compounds of formula I display pharmacological activity in test procedures designated to indicate m1 and m2 muscarinic antagonist activity. The compounds are non-toxic at pharmaceutically therapeutic doses. Following are descriptions of the test procedures.

MUSCARINIC BINDING ACTIVITY

The compound of interest is tested for its ability to inhibit binding to the cloned human m1, m2, m3, and m4 muscarinic receptor subtypes. The sources of receptors in these studies were membranes from stably transfected CHO cell lines which were expressing each of the receptor subtypes. Following growth, the cells were pelleted and subsequently homogenized using a Polytron in 50 volumes cold 10 mM Na/K phosphate buffer, pH 7.4 (Buffer B). The homgenates were centrifuged at 40,000 x g for 20 minutes at 4°C. The resulting supernatants were discarded and the pellets were resuspended in Buffer B at a final concentration of 20 mg wet tissue/ml. These membranes were stored at -80°C until utilized in the binding assays described below.

Binding to the cloned human muscarinic receptors was performed using ^{3}H-quinuclidinyl benzilate (QNB) (Watson et al., 1986). Briefly, membranes (approximately 8, 20, and 14 µg of protein assay for the m1, m2, and m4 containing membranes, respectively) were incubated with ^{3}H-QNB (final concentration of 100-200 pM) and increasing concentrations of unlabeled drug in a final volume of 2 ml at 25°C for 90 minutes. Non-specific binding was assayed in the presence of 1 µM atropine. The incubations were terminated by vacuum filtration over GF/B glass fiber filters using a Skatron filtration apparatus and the

filters were washed with cold 10mM Na/K phosphate butter, pH 7.4. Scintillation cocktail was added to the filters and the vials were incubated overnight. The bound radioligand was quantified in a liquid scintillation counter (50% efficiency). The resulting data were analyzed for IC_{50} values (i.e. the concentration of compound required to inhibit binding by 50%) using the EBDA computer program (McPherson, 1985). Affinity values (K_i) were then determined using the following formula (Cheng and Prusoff, 1973);

$$K_i = \frac{IC_{50}}{1+\left[\frac{\text{concentration of radioligand}}{\text{affinity } (K_D) \text{ of radioligand}}\right]}$$

Hence a lower value of K_i indicates greater binding affinity.

The following publications, the entire contents of which are incorporated herein by reference, explain the procedure in more detail.

Cheng, Y.-C. and Prusoff, W.H., Relationship between the inhibitory constant (K_i) and the concentration of inhibitor which causes 50 per cent inhibition (IC_{50}) of an enzymatic reaction. Biochem. Pharmacol. 22: 3099-3108, 1973.

McPherson, G.A. Kinetic, EBDA, Ligand, Lowry: A Collection of Radioligand Binding Analysis Programs. Elsevier Science Publishers BV, Amsterdam, 1985.

Watson, M.J, Roeske, W.R. and Yamamura, H.I. [^{3}H] Pirenzepine and (-)[^{3}H)quinuclidinyl benzilate binding to rat cerebral cortical and cardiac muscarinic cholinergic sites. Characterization and regulation of antagonist binding to putative muscarinic subtypes. J. Pharmacol. Exp. Ther. 237: 411-418, 1986.

To determine the degree of selectivity of a compound for binding the m2 receptor, the K_i value for m1 receptors was divided by the K_i value for m2

receptors. A higher ratio indicates a greater selectivity for binding the m2 muscarinic receptor.

MICRODIALYSIS METHODOLOGY

The following procedure is used to show that a compound functions as an m2 antagonist.

Surgery: For these studies, male Sprague-Dawley Rats (250-350 g) were anesthetized with sodium pentobarbital (54 mg/kg, ip) and placed on a Kopf sterotaxic apparatus. The skull was exposed and drilled through to the dura at a point 0.2 mm anterior and 3.0 mm lateral to the bregma. At these coordinates, a guide cannula was positioned at the outer edge of the dura through the drilled opening, lowered perpendicularly to a depth of 2.5 mm, and permanently secured with dental cement to bone screws. Following the surgery, rats were given ampicillin (40 mg/kg, ip) and individually housed in modified cages. A recovery period of approximately 3 to 7 days was allowed before the microdialysis procedure was undertaken.

Microdialysis: All of the equipment and instrumentation used to conduct in vivo microdialysis was obtained from Bioanalytical Systems, Inc. (BAS). The microdialysis procedure involved the insertion through the guide cannula of a thin, needle-like perfusable probe (CMA/12,3 mm x 0.5 mm) to a depth of 3 mm in striatum beyond the end of the guide. The probe was connected beforehand with tubing to a microinjection pump (CMA-/100). Rats were collared, tethered, and, following probe insertion, were placed in a large, clear, plexiglass bowl with litter material and access to food and water. The probe was perfused at 2 µl/min with Ringer's buffer (NaCl 147 mM; KCl 3.0 mM; $CaCl_2$ 1.2 mM; $MgCl_2$ 1.0 mM) containing 5.5 mM glucose, 0.2 mM L-ascorbate, and 1 µM neostigmine

bromide at pH 7.4). To achieve stable baseline readings, microdialysis was allowed to proceed for 90 minutes prior to the collection of fractions. Fractions (20 µl) were obtained at 10 minute intervals over a 3 hour period using a refrigerated collector (CMA/170 or 200). Four to five baseline fractions were collected, following which the drug or combination of drugs to be tested was administered to the animal. Upon completion of the collection, each rat was autopsied to determine accuracy of probe placement.

Acetylcholine (ACh) analysis: The concentration of ACh in collected samples of microdialysate was determined using HPLC/electrochemical detection. Samples were auto-injected (Waters 712 Refrigerated Sample Processor) onto a polymeric analytical HPLC column (BAS, MF-6150) and eluted with 50 mM Na_2HPO_4, pH 8.5. To prevent bacterial growth, Kathon CG reagent (0.005%) (BAS) was included in the mobile phase. Eluent from the analytical column, containing separated ACh and choline, was then immediately passed through an immobilized enzyme reactor cartridge (BAS, MF-6151) coupled to the column outlet. The reactor contained both acetylcholinesterase and choline oxidase covalently bound to a polymeric backbone. The action of these enzymes on ACh and choline resulted in stoichiometric yields of hydrogen peroxide, which was electrochemically detected using a Waters 460 detector equipped with a platinum electrode at a working potential of 500 mvolts. Data acquisition was carried out using an IBM Model 70 computer equipped with a microchannel IEEE board. Integration and quantification of peaks were accomplished using "Maxima" chromatography software (Waters Corporation). Total run time per sample was 11 minutes at a flow rate of 1 ml/min. Retention times for acetylcholine and choline were 6.5 and 7.8 minutes, respectively. To monitor and correct for possible changes in detector sensitivity during chromatography, ACh standards were included at the beginning, middle and end of each sample queue.

Increases in ACh levels are consistent with presynaptic m2 receptor antagonism.

RESULTS OF THE TESTS

For compoud numbers 169, 227(-), 289, 269, 214, 232, 123, 236, 296, 300, 301, 302, 304, and 305:

Ki, nM, m1: 2.1 to 224

Ki, nM, m2: 0.05 to 16.6

m2 selectivity ration (Ki, m1/Ki, m2) = 9.3 to 42

Ki, nM, m4: 0.33 to 36

m4 selectivity ration (Ki, m1/Ki, m4): 3 to 12

Numerous other compounds in accordance with formula I were tested with the following range of results:

K_i binding to m1 receptor, nM: 0.01 to 4770 with undetermined values up to > 4200. An undetermined value occurred when a K_i was not completely determined, but was found to be above some value of up to 4200 nM.

K_i binding to m2 receptor, nM: 0.01 to 1525 with undetermined values up to > 4600. An undetermined value occurred when a K_i was not completely determined, but was found to be above some value of up to 4600 nM.

m2 Selectivity Ratio [K_i for m1/K_i for m2]

0.3 to 41.5 without regard to any undetermined K_i values.

When compound No. 169 from the table of compounds was administered the following increases in ACh release above baseline levels were measured.

From Cortex of Conscious Rat (i.p. administration)

Dosage mg/kg (Compound 169)	Peak ACh release as % increase over Baseline (Figure 1)
30	1500
10	400
1	75

From Striatum of Conscious Rat (i.p. Administration)

Dosage mg/kg (Compound 169)	Peak ACh release as % increase over Baseline (Figure 2)
30	270
10	150
3	125
1	30
0.1	10

Oral administration of compound 169 also caused a significant increase in ACh release.

We have made the surprising discovery that compounds of formula I in combination with an acetylcholinesterase (ACh' ase) inhibitor have a synergistic effect on ACh release, as shown below. Here Tacrine was used as the ACh'ase inhibitor.

From Striatum of Conscious Rat

Dose	Peak ACh release as % increase over Baseline (Figures 3 to 5)
Tacrine 3 mg/kg (i.p.)	30 (figure 3)
Compound 169 1 mg/kg (i.p.)	40 (figure 4)
Tacrine 3 mg/kg and Compound 169 1 mg/kg (i.p.)	130 (figure 5)

As shown immediately above, when administered in combination, compound 169 and tacrine produce a synergistic increase in ACh release.

The present invention also relates to achieving similar synergistic results by administering a compound of formula I in combination with any other ACh' ase inhibitor including, but not limited to, E-2020 (available from Eisai Pharmaceutical) and heptylphysostigmine.

The present invention also relates to achieving similar synergistic results by administering any compound capable of enhancing ACh release, such as scopolamine or QNB in combination with an ACh'ase inhibitor. Preferably the ACh release enhancing compound is an m2 selective muscarinic antagonist, i.e. one having a (K_i for m1/K_i for m2) ratio greater than 1 or an m4 selective muscarinic antagonist (Ki for m1/Ki for m4 greater than 1). The m2 or m4 selective muscarinic antagonists for practicing this aspect of the invention include without limitation 3-α-chloroimperialine, AF-DX 116, AF-DX 384, BIBN 99 (these three compounds being available from Boehringer-Ingleheim), tripitramine, and himbacine.

For preparing pharmaceutical compositions from the compounds of formula I, compounds capable of enhancing ACh release, and ACh'ase inhibitors, pharmaceutically acceptable, inert carriers are admixed with the active compounds. The pharmaceutically acceptable carriers may be either solid or

liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier can be one or more substances which may also act as dilutents, flavoring agents, solubilizers, lubricants, suspending agents, binders or tablet disintegrating agents; it may also be an encapsulating material.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parentertal administration. Such liquid forms include solutions, suspensions and emulsions. These particular solid form preparations are most conveniently provided in unit dose form and as such are used to provide a single liquid dosage unit.

The invention also contemplates alternative delivery systems including, but not necessarily limited to, transdermal delivery. The transdermal compositions can take the form of creams, lotions and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active components. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation such as packeted tablets, capsules and powders in vials or ampules. The unit dosage form can also be a capsule, cachet or tablet itself, or it may be the appropriate number of any of these in a packaged form.

The quantity of active compound in a unit dose preparation may be varied or adjusted from 1 mg to 100 mg according to the particular application and

the potency of the active ingredient and the intended treatment. This would correspond to a dose of about 0.001 to about 20 mg/kg which may be divided over 1 to 3 administrations per day. The composition may, if desired, also contain other therapeutic agents.

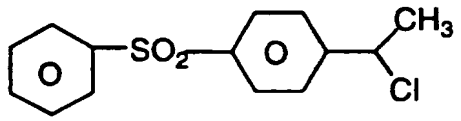
The dosages may be varied depending on the requirement of the patient, the severity of the condition being treating and the particular compound being employed. Determination of the proper dosage for a particular situation is within the skill of those in the medical art. For convenience, the total daily dosage may be divided and administered in portions throughout the day or by means providing continuous delivery.

When a compound of formula I or a compound capable of enhancing ACh release is used in combination with an acetylcholinesterase inhibitor to treat cognitive disorders these two active components may be co-administered simultaneously or sequentially, or a single pharmaceutical composition comprising a compound of formula I or a compound capable of enhancing ACh release and an acetylcholinesterase inhibitor in a pharmaceutically acceptable carrier can be administered. The components of the combination can be administered individually or together in any conventional oral or parenteral dosage form such as capsule, tablet, powder, cachet, suspension, solution, suppository, nasal spray, etc. The dosage of the acetylcholinesterase inhibitor may range from 0.001 to 100 mg/kg body weight.

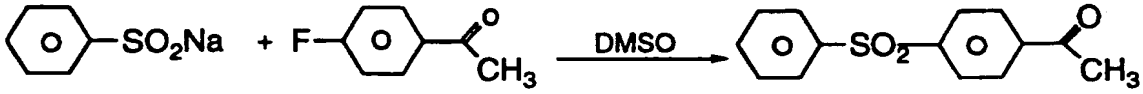
The invention disclosed herein is exemplified by the following preparation and examples which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures may be apparent to those skilled in the art.

PREPARATIONS

Preparation 1

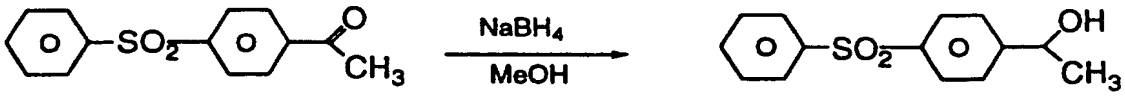


II'



1 2 3

21.4g (130 mmol) of 1 and 15.0g (108.6 mmol) of 2 were placed in a round bottom flask. DMSO (100 ml) was added and the mixture was warmed to 130°C where it was stirred for 70 hours. The reaction was cooled and poured into 400g of ice and stirred thoroughly. The mixture was filtered and a white precipitate was collected which was washed with water. The solid was recrystallized from ethanol.



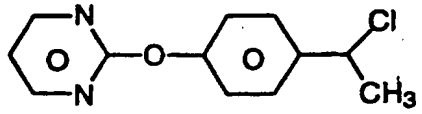
3 4

Compound 3 (13.72g, 52.7 mmol) was dissolved in methanol (100 ml) and cooled to 0°C where $NaBH_4$ (1.2g, 31.6 mmol) was added in small portions. The mixture was stirred for one half hour, then warmed to reflux, stirred for 4 hours, and cooled to room temperature. The solvent was removed on a rotary evaporator. The residue was dissolved in ethyl acetate (400 ml) and washed with water and brine, dried over Na_2SO_4 and then filtered. The solvent was removed with a rotary evaporator.

4 II'

A CH_2Cl_2 (120 ml) solution of 4 (14g, 53 mmol) was cooled to 0°C and $SOCl_2$ (7.8 ml, 107 mmol), in 20 ml CH_2Cl_2 was added over a 30 minute period. The mixture was warmed to room temperature and stirred overnight. The volatiles were removed on a rotary evaporator and the residue dissolved in 500 ml ethyl acetate. The organic solution was washed with water, saturated with $NaHCO_3$, and brine. The mixture was dried over Na_2SO_4, filtered and the solvent was removed on a rotary evaporator.

Preparation 2



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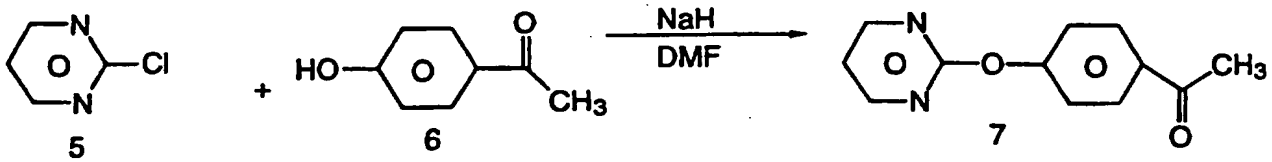
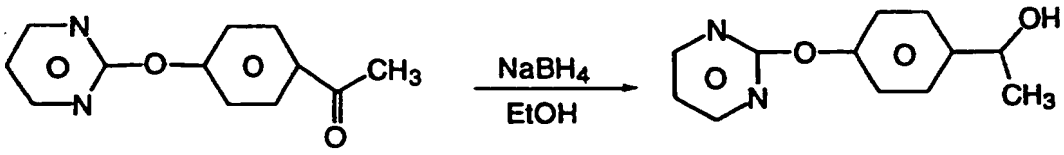


5 6 7

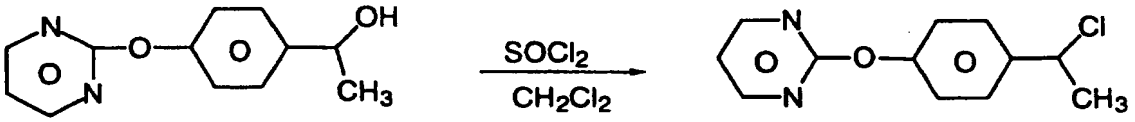
Compound 6 (25g, 180 mmol) was dissolved in 80 ml DMF and cooled to 0°C. Sodium hydride (7.2g 60% dispersion in mineral oil) was added under nitrogen. Stirring was continued for 20 minutes then the reaction mixture was warmed to room temperature when compound 5 (20g, 180 mmol), dissolved in 40 ml DMF, was added with syringe. The solution was heated to 100°C and stirred for 3 hours, then cooled to room temperature. DMF was removed with a

rotary evaporator, then 250 ml water was added and the pH adjusted with NaOH to 12. The solution was extracted with ethyl acetate, dried over Na_2SO_4 and filtered. The solvent was then removed with a rotary evaporator.



7 8

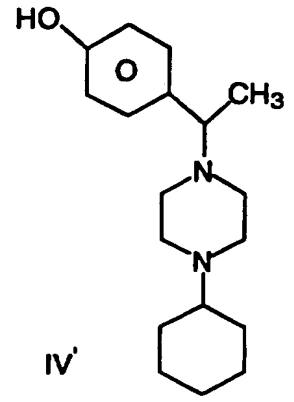
Compound 7 (22g, 100 mmol) was dissolved in 450 ml EtOH, and cooled to 0°C. $NaBH_4$ (1.9g, 51 mmol) was added in portions. The mixture was warmed to room temperature and stirred overnight. Water (300 ml) was added and then removed on a rotary evaporator. Ethyl acetate was added to the residue which was then washed with water. The organic layer was dried over Na_2SO_4, filtered, and removed with a rotary evaporator.



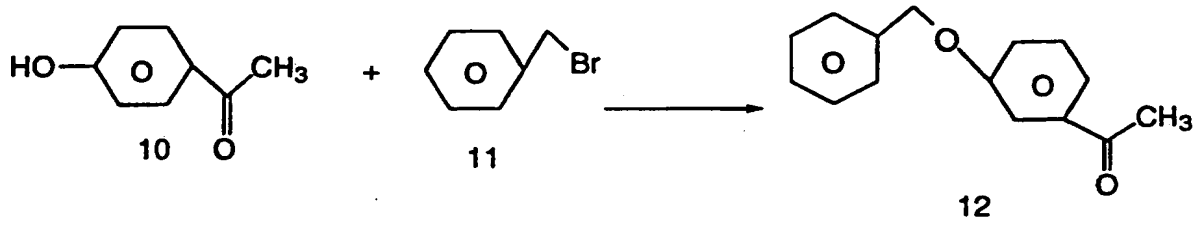
8 9

Compound 8 (22g, 100 mmol) was dissolved in 400 ml CH_2Cl_2 and cooled to 0°C. $SOCl_2$ (9 ml, 120 mmol) was dissolved in CH_2Cl_2 (50 ml) and added to compound 8 with a dropping funnel, under nitrogen. After addition was complete, the mixture was stirred at 0°C for 1/2 an hour, then at room temperature for 2 hours. The solution was decanted into an Erlenmeyer flask to remove the precipitate. 10% $NaHCO_3$ was added until the pH of the aqueous layer was 8. The layers were separated and the CH_2Cl_2 layer was dried with $MgSO_4$. The layer was then filtered and the solvent was removed on a rotary evaporator.

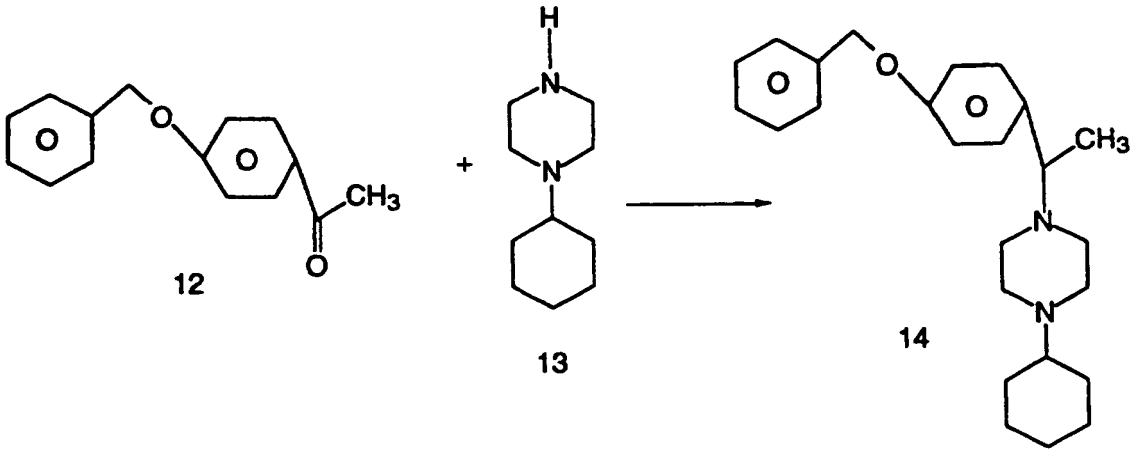
Preparation 3



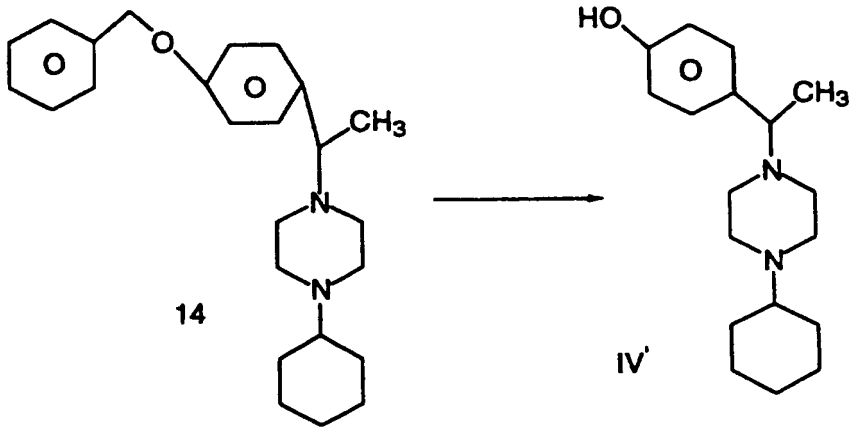
IV'



Compound 10 (54g, 400 mmol) was dissolved in 500 ml DMF and cooled to 0°C. $NaOCH_3$ (20.5g) was added in portions with stirring. The ice bath was removed and compound 11 (68.4g, 400 mmol) was added with stirring. The mixture stirred at room temperature for 3 hours, then at 80°C for 1 hour, and cooled to room temperature. The DMF solution was concentrated to 200 ml, then 400 ml water and 300 ml ethyl acetate was added with stirring by a mechanical stirrer. The pH was made basic with NaOH, and the organic layer was separated, and dried over $MgSO_4$. The solution was filtered and the solvent was then removed by a rotary evaporator.



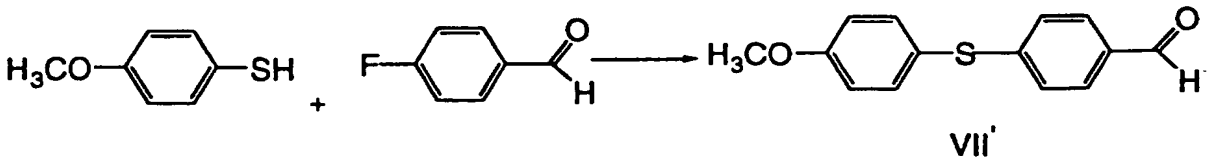
Compound 12 (33.4g, 147 mmol) was dissolved in 1L CH_2Cl_2. Compound 13 (25g, 148 mmol) and triethylamine (21 ml) were added next. To this solution was added $TiCl_4$ (75 ml of a 1M CH_2Cl_2 solution). Stirring was continued at room temperature overnight (18h). The reaction was quenched with a solution of $NaCNBH_3$ (27g, 440 mmol, in 150 ml MeOH). After stirring for 2-3 hours, water was added and the pH adjusted to 13 with NaOH. The organic layer was separated and dried over $MgSO_4$, followed filtration and removal of the solvent. The residue was dissolved in ethyl acetate and extracted with 3N HCl. The layers were separated and the aqueous layer was basified with NaOH (pH = 13). CH_2Cl_2 was used to extract the aqueous layer. The CH_2Cl_2 layer was then dried over $MgSO_4$, filtered and evaporated to give compound 14.



Ethanol (300 ml) was added to compound 14 (17g, 45 mmol), followed by 2.5g $Pd(OH)_2/C$. The mixture was placed on a Parr shaker for 1 to 8 hours monitored by TLC at 60 psi of hydrogen then filtered through Celite and the EtOH was removed. The residue was dissolved in ethyl acetate and washed in NaOH. The pH of the aqueous layer was then adjusted to 7, then the aqueous layer was extracted with CH_2Cl_2, dried with Na_2SO_4, then evaporated to produce compound IV'. This was then recrystalized from CH_3CN to produce pure IV'.

Preparation 4

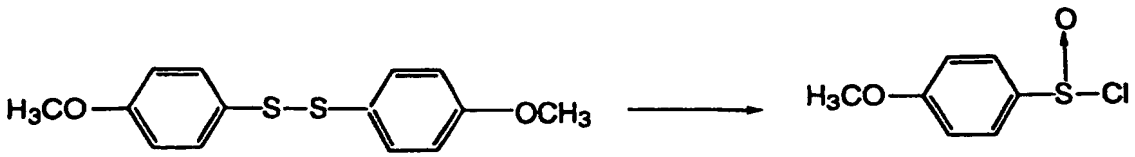
(Process C)



VII'

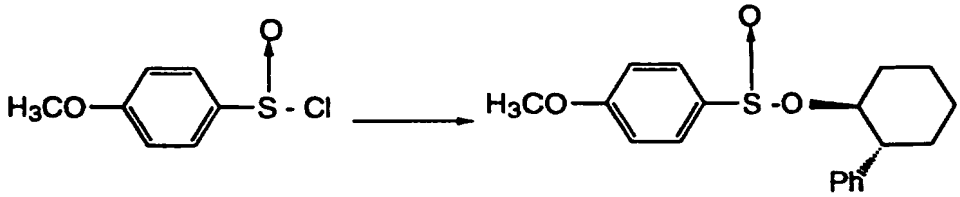
4.3 g (1 equivalent) of 60% sodium hydride dispersion in mineral oil was weighed into a flame-dried 250 ml flask under nitrogen. The mineral oil was removed by washing with hexane, and 100 ml of dry N,N-dimethylformamide was added by syringe. The suspension was cooled in an ice water bath while 15g (1 equiv.) of 4-methoxythiophenol was added in portions. The mixture was stirred for 1 hour at room temperature after addition was complete, and 14.6g (12.6 mL, 1.1 equiv.) of 4-fluorobenzaldehyde was added in one portion. The mixture was stirred for 3 days at room temperature, then poured slowly into 600 mL of ice water with vigorous stirring. The yellow solid was separated by filtration, then triturated twice with 150 mL portions of hexane by vigorous stirring. The product obtained is a light yellow powder, 23 g (88% yield), sufficiently pure for further reaction.

Preparation 5



6.75 grams of bis(paramethoxyphenyl)disulfide were stirred with 3.6 mL of glacial acetic acid, and the mixture was cooled to -40°C. Sulfuryl chloride (7.5 mL) was added in portions, and the solution was maintained at -40°C while the solid dissolved. The brown solution was warmed gradually to -20°C and stirred for five hours, then warmed to 0°C. Gas was evolved during this period, and the solution darkened to green. The volatiles were removed *in vacuo*, and the crude material was used in the next reaction without delay.

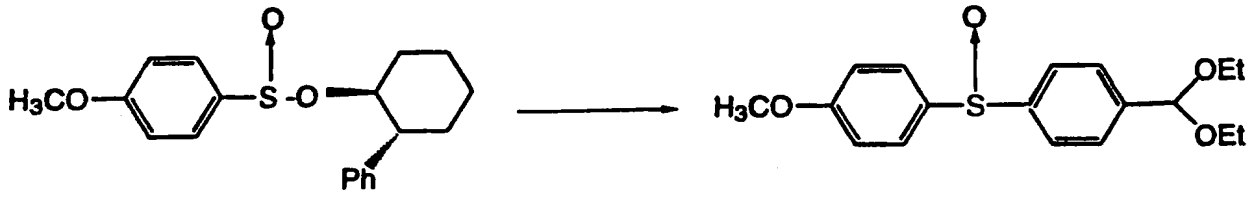
Preparation 6



6.9 grams (39.1 mm) of (1R,2S)-2-phenylcyclohexanol (prepared in accordance with J.K. Whitesell, M-S Wong, J. Org. Chem, 56(14), p. 4552, 1991) were dissolved in 150 mL dry THF with 6 mL dry pyridine. The solution was cooled to -78°C, and para-methoxyphenyl sulfinyl chloride (derived from 6.75 g of the corresponding disulfide) was added slowly. The solution developed a white precipitate as it was stirred at -78°C for one hour. The reaction was quenched with saturated sodium bicarbonate, diluted with ethyl acetate, and extracted with bicarbonate solution and brine. The organic layers were dried over sodium sulfate, concentrated, and purified by column chromatography in a gradient of 10% ethyl acetate/hexane to 25% ethyl acetate/hexane, yielding 10 grams (78%) of the desired sulfinate, slightly contaminated with the minor diastereomer. This

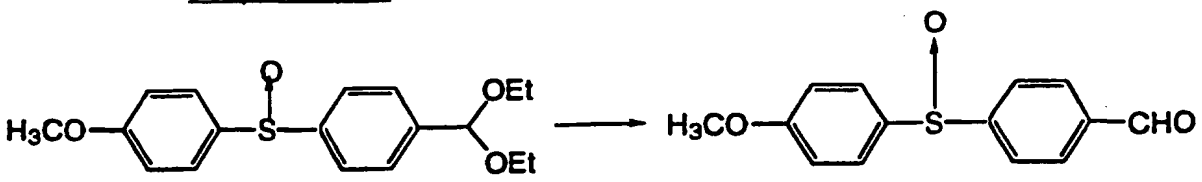
diastereomer was purified by crystallization from hexane/ethyl acetate, a procedure also applicable to the crude product.

Preparation 7



1.25 grams of magnesium turnings (52 mm, 2.3 equivalents) were stirred in 5 mL of dry THF. One drop of 1,2-dibromoethane was added, followed by a small portion (roughly one gram) of 4-bromobenzaldehyde diethyl acetal. The solution was heated to initiate formation of the Grignard reagent, and the remaining acetal (to a total of 11.2 grams, 45 mm, 2 equivalents) was added in portions, along with THF (to a total of 25 mL.) The mixture was heated to reflux for 45 minutes, then cooled to room temperature. The Grignard solution thus obtained was added in portions to a solution of the starting sulfinate ester (7.5 grams, 22.6 mm) in 150 mL dry toluene at 0°C. After one hour, the reaction was quenched with saturated sodium bicarbonate solution, diluted with ethyl acetate, and extracted with brine. The organic layers were dried over sodium sulfate, concentrated, and purified by brief column chomatography in 25% ethyl acetate/hexane to give recovered chiral alcohol and the desired acetal, which was used directly in the next reaction.

Preparation 8



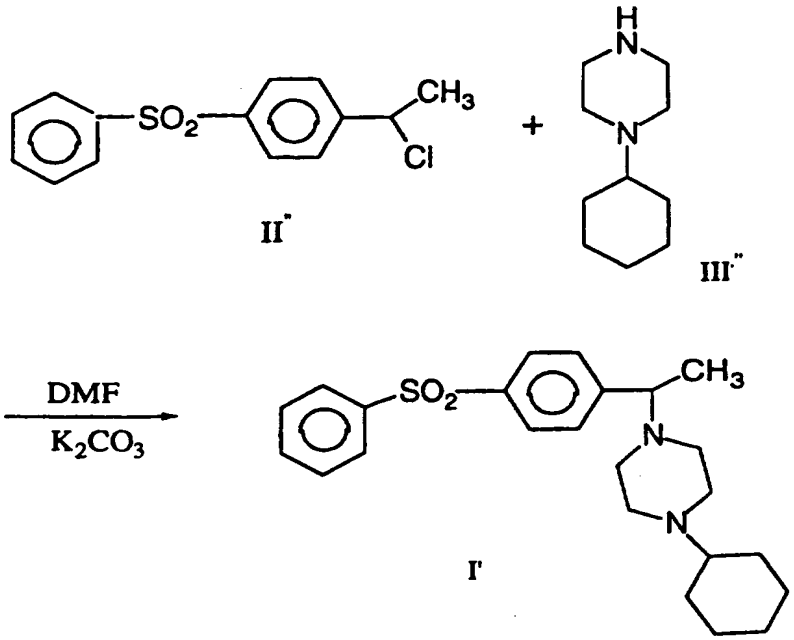
The acetal obtained from the reaction of 7.5 grams of sulfinate ester was taken up in 60 mL of THF with 10 mL distilled water. A catalytic amount of paratoluene sulfonic acid was added, and the solution was warmed to 60°. After three hours, the mixture was cooled to room temperature, diluted with ethyl acetate, and extracted with saturated sodium bicarbonate solution. The organic layers were dried over sodium sulfate and concentrated to give the desired aldehyde as a crystalline solid, 5.42 grams (97% over two steps).

Preparation 9

2 grams (8.17 mm) of the starting 4-(4-methoxyphenyl)thiobenzaldeyde and 1.75 g (1 equivalent of 80%) meta-chloroperbenzoic acid were taken up in 40 mL of dichloromethane at 0°. After 30 minutes, 300 mg of additional MCPBA was added, and the reaction stirred 30 minutes more. The solution was diluted with ethyl acetate and extracted with saturated sodium bicarbonate. The organic layers were dried over sodium sulfate, concentrated, and the product was crystallized from ethyl acetate/hexane to give a first crop of 1.65 grams.

EXAMPLE 1

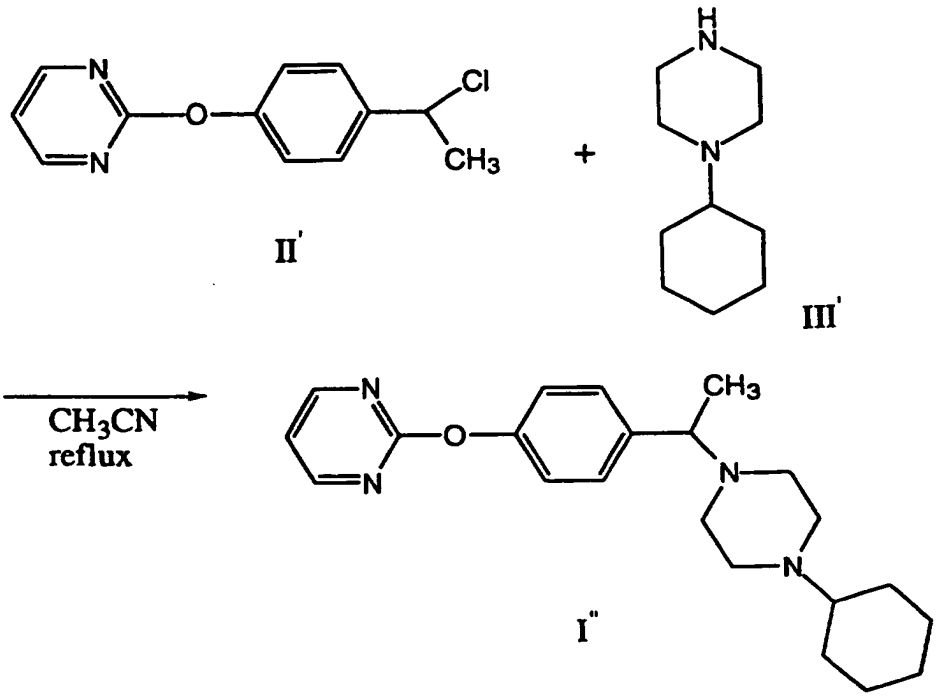
(Process A)



Compound II' (1.0g, 3.5 mmol) was dissovled in DMF (10 ml), followed by addition of K_2CO_3 (1.5g). Compound III' (0.66g, 3.9 mmol) was next added. The mixture was warmed to 50°C and maintained for 18 hours with stirring. The mixture was cooled to room temperature and ethyl acetate (EtOAc) (150 ml) was added. The organic layer was washed with water (5 x 50 ml) and saturated NaCl (1 x 25 ml). The organic layer was dried over Na_2SO_4, filtered, and the volatiles removed with a rotary evaporator. The resulting oil was purified by column chromatography, on silica gel, with ethyl acetate as solvent.

EXAMPLE 2

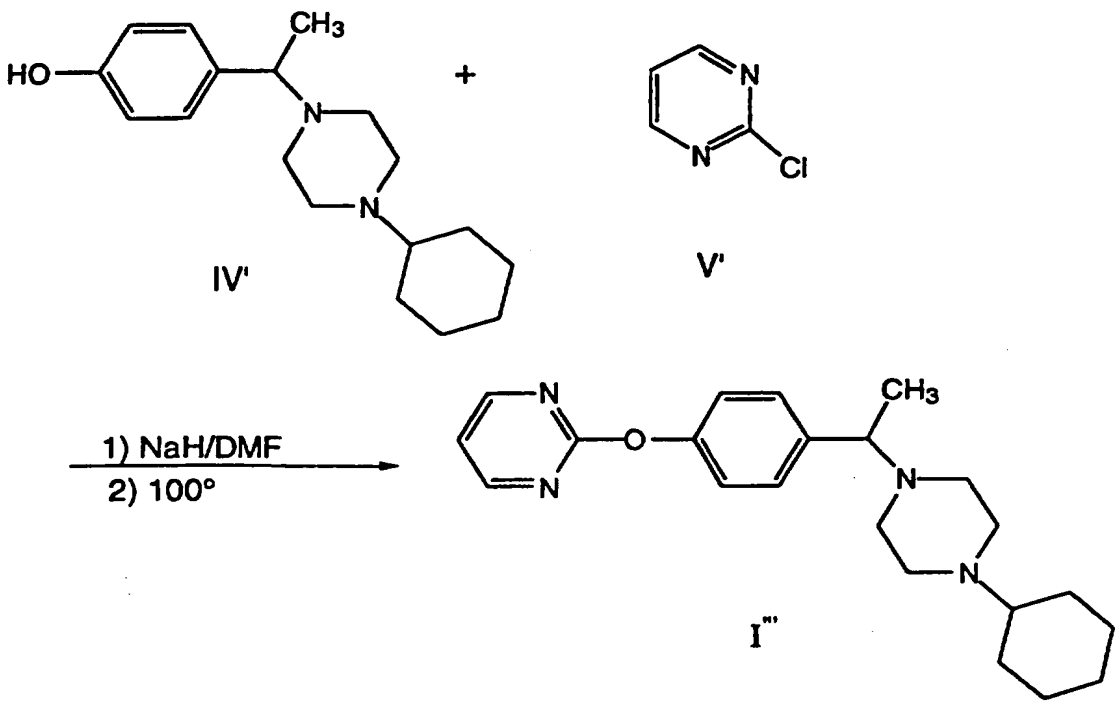
(Process A)



To the solid chloride (770 mg) was added a solution of 2 equivalents of cyclohexylpiperazine in 5 mL CH_3CN. The mixture was heated with stirring at reflux for 2 hours then allowed to stand for 18 hours. The resulting solid was suspended in 1:1 EtOAc : water. The aqueous layer was basified with solid K_2CO_3. The organic layer was washed several times with water, dried with $MgSO_4$ and evaporated to obtain the crude product. This was purified by chromatography on a column of silica gel, (TLC grade), and 50:3:1 CH_2Cl_2:EtOH:NH_4OH as the eluant.

EXAMPLE 3

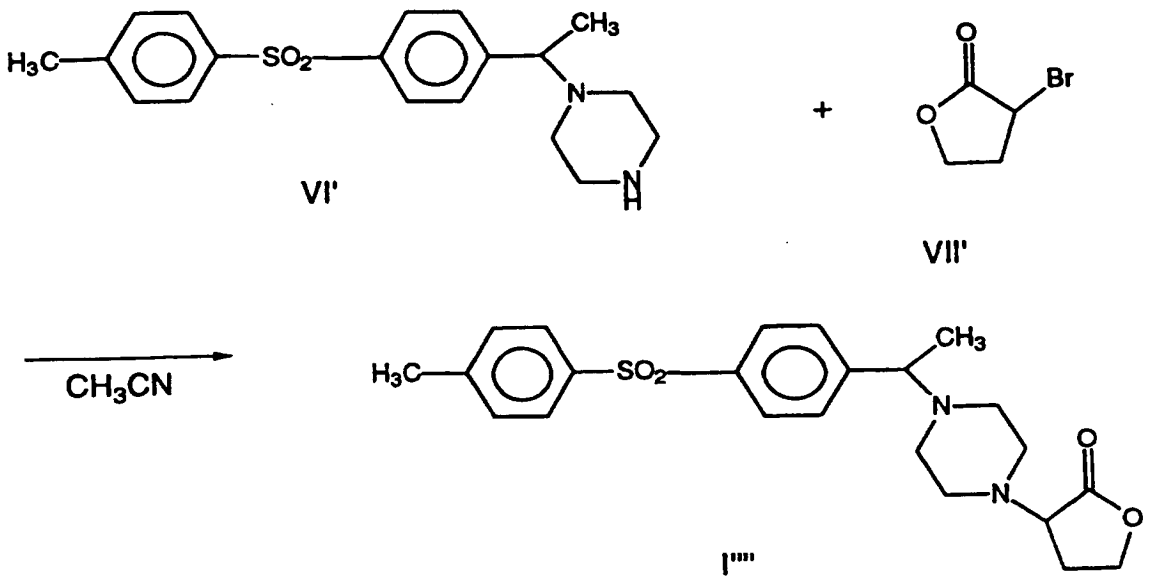
(Process B)



To an ice cold solution of compound IV' (1 equivalent) in dry DMF under nitrogen was added 0.9 equivalents of NaH, (60% dispersion in mineral oil). After 20 minutes 2-chloropyrimidine was added (0.9 equivalents). The solution was heated at 100°C for 4 hours. After cooling to room temperature water was added (10 mls per 1 ml DMF) and the solution extracted with ethyl acetate. The organic extracts were dried with $MgSO_4$ and evaporated to obtain the crude product which was then purified by column chromatography, (Silica gel, TLC grade and 50:3:1 CH_2Cl_2:EtOH:NH_4OH as eluant).

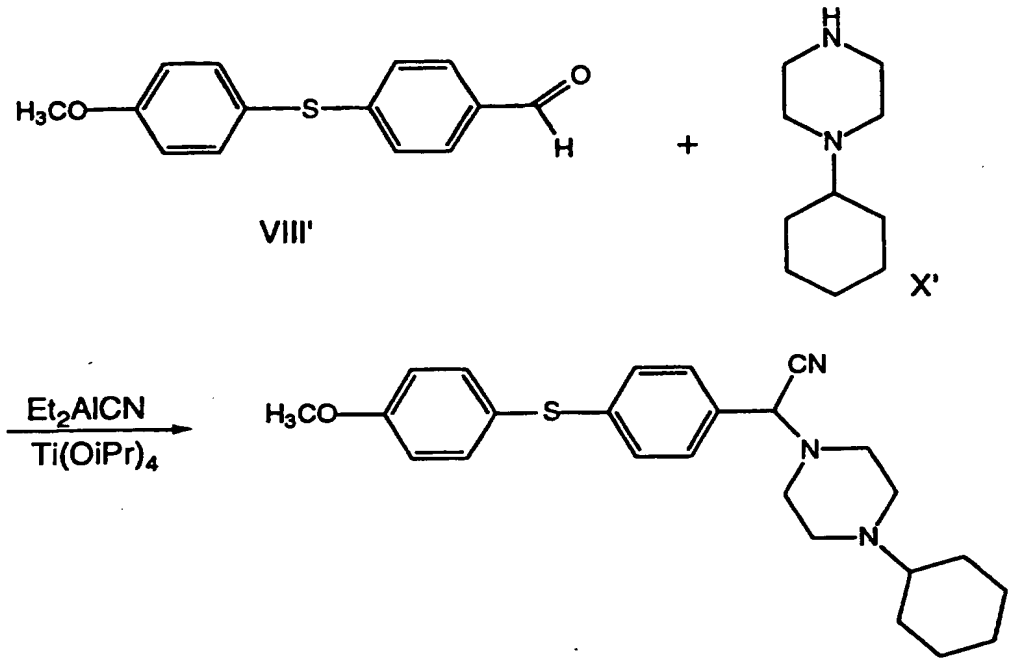
Example 4

(Process C)



To a solution of VI' (0.25g, 0.73 mmol) in 5 ml acetonitrile was added a solution of VII' (0.12g, 0.73 mmol, dissolved in 3 ml acetonitrile). The mixture was stirred at room temperature (20°C) for 0.5 hours, then warmed to 45°C and stirred for 6 hours. The mixture was cooled to room temperature and ethyl acetate (150 ml) was added and the organic layer was washed with saturated NaCl (1 x 50 ml). The organic layer was dried over Na_2SO_4. The organic layer was filtered and the volatiles removed with a rotary evaporator. The resulting oil was purified by flash chromatography using 50 g silica gel and 9 : 1 CH_2Cl_2/MeOH (saturated with NH_4OH) as solvent. 0.19g of a syrup was collected.

Example 5 (process D)

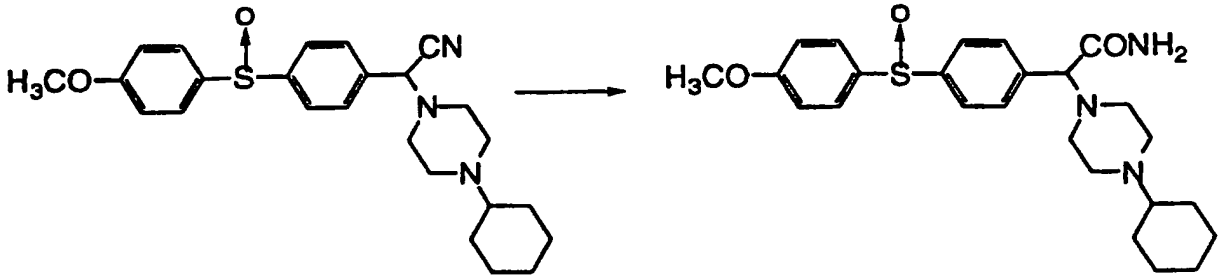


2 grams (8.17 mmol) of the starting 4-(4-methoxyphenyl)thiobenzaldehyde, VIII', and 1.65g (10 ml, 1.2 equivalents) of N-cyclohexylpiperazine, X', were taken up under a nitrogen atmosphere in 1 mL of dry dichloromethane at room temperature. 2.9 mL (10 mmol, 1.2 equivalents) of titanium tetraisopropoxide were added by syringe, and the resulting solution was stirred at room temperature for 18 hours. The reaction developed a white precipitate during this period. The reaction was cooled in an ice water bath while 16.3 mL of a 1 molar toluene solution (2 equivalents) of diethylaluminum cyanide were added in portions by syringe. The resulting homogeneous red/brown solution was stirred for 30 minutes at room temperature. The reaction was diluted by the addition of 100 mL ethyl acetate, and quenched by the slow addition of 25 mL water, with vigorous stirring. After 1 hour, the inorganic solids were removed by filtration through Celite, and the filtrate was washed with a saturated brine solution and dried by anhydrous sodium sulfate. The product was concentrated,

then purified by column chromatography in a gradient of acetate/hexane, yielding 3.29 grams of the desired product (95% yield.)

Example 6

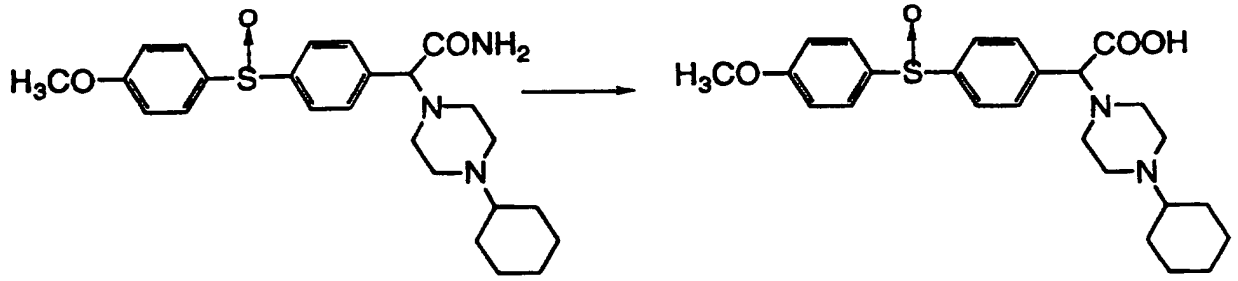
Hydrolysis of cyano compound to amide



2 grams (4.6 mm) of the starting nitrile were stirred in 25 mL of tertiary butanol with 1.2 grams (21 mm) of powdered potassium hydroxide. The mixture was heated to reflux for 30 minutes, cooled to room temperature, and diluted with 250 mL of water. The solution was extracted twice with ethyl acetate, and the organic layers were dried over sodium sulfate. Evaporation gave the amide (2 grams, 96%) as an amorphous solid which can be used in subsequent reactions without further purification.

Example 7

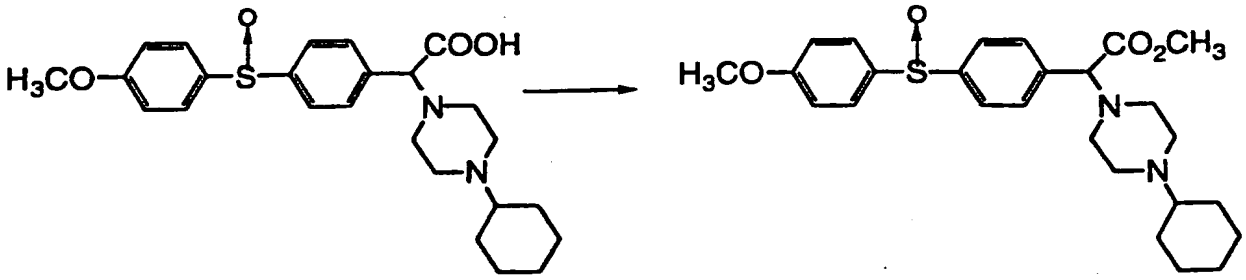
Hydrolysis of amide to acid



0.95 grams of starting amide (2.1 mm) were taken up in 20 mL of 4N hydrochloric acid. The reaction was heated to reflux for 16 hours. The volume of the solution was reduced *in vacuo*, whereupon the dihydrochloride salt of the desired product precipitated. The solid was isolated by filtration and washed with dry ethyl ether to give 0.85 grams of product, 77% yield. This solid was suitable for use without further purification.

Example 8

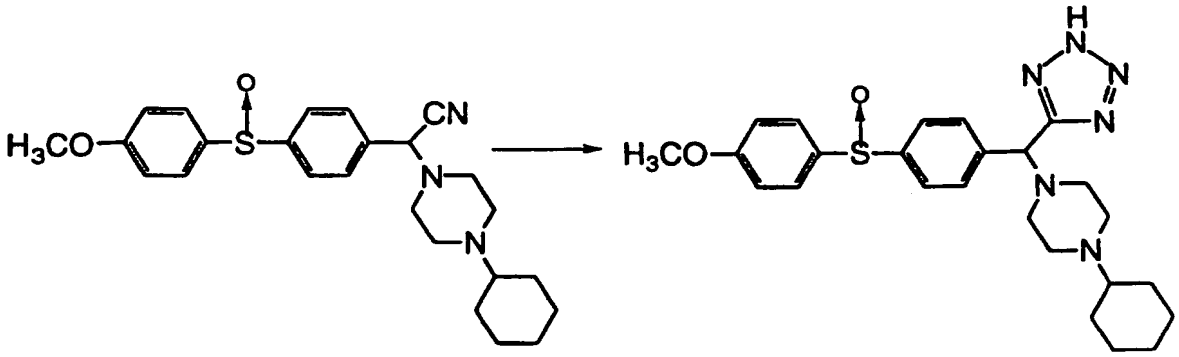
Formation of Methyl Ester



A solution of methanolic HCl was prepared by the addition of 3 mL of acetyl chloride to 50 mL of dry methanol. To this solution was added 400 milligrams (0.88 mm) of the starting acid. The flask was fitted with a Soxhlet extraction thimble containing freshly activated molecular sieves (3 Å), and the solution was heated to reflux for 16 hours. The reaction was cooled to room temperature, and the acid was neutralized with solid sodium carbonate. The solution was diluted with 300 mL of dichloromethane and washed with distilled water. The organic layers were dried over magnesium sulfate and purified by column chromotography in 3% methanol/dichloromethane to give 310 milligrams (76%) of the desired product.

Example 9

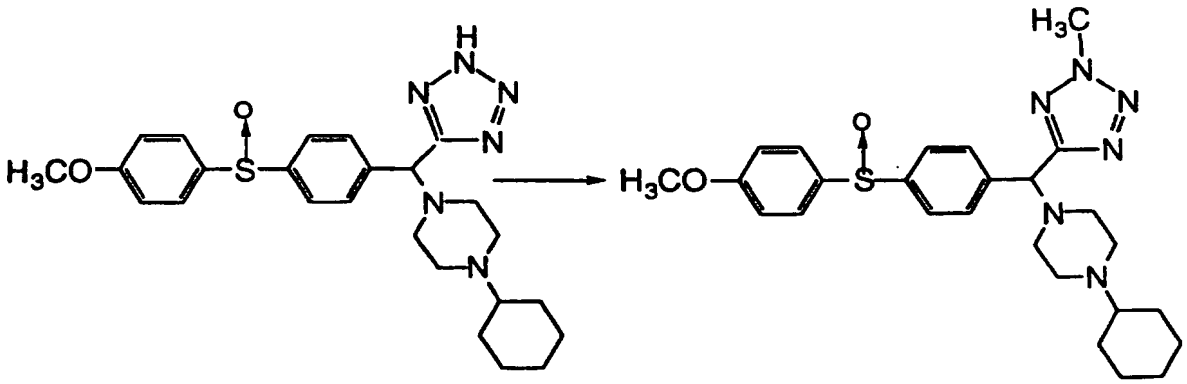
Formation of tetrazole



250 milligrams (0.57 mm) of the starting nitrile were taken up under a nitrogen atmosphere in 4 mL of dry toluene with 0.15 mL trimethylsilyl azide (2 equivalents) and 14 milligrams of dibutyltin oxide (1 equivalent). The solution was heated at 100° for 48 hours, whereupon additional equivalents of the azide and tin reagents were added and the solution was heated an additional 24 hours. The reaction was cooled to room temperature and evaporated to a brown solid, which was purified by preparative thin-layer chromatography in 20% methanol/dichloromethane. 27 milligrams of the desired tetrazole were isolated.

Example 10

Alkylation of tetrazole



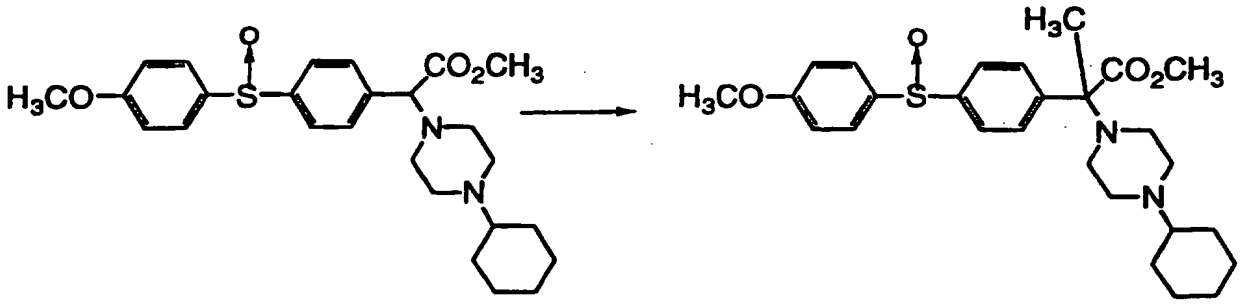
20 milligrams (0.57 mm) of the starting tetrazole were treated with an ethereal solution of diazomethane (excess) at 0°. The solution became homogeneous after ten minutes, and after an additional thirty minutes the solution

was evaporated and purified by preparative thin-layer chromatograpy in 7.5% methanol/dichloromethane. 10 milligrams of product were isolated.

Example 11

(Process E)

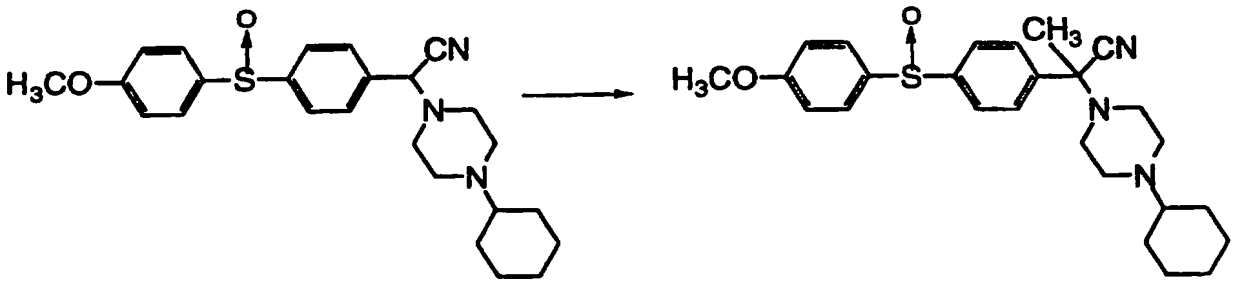
Alkylation of methyl ester



100 milligrams (0.2 mm) of the starting ester were taken up under a nitrogen atmosphere in 4 mL of dry tetrahydrofuran at 0°. 0.53 mL (0.26 mm, 1.3 equivalents) of potassium hexamethyldisilazide solution (0.5 M in toluene) were added by syringe, and the resulting solution was stirred for ten minutes. 0.02 mL of iodomethane (1.3 equivalents) were then added by syringe The reaction was stirred for 20 minutes while warming to room temperature, then diluted by the addition of 50 mL ethyl acetate, and extracted with saturated sodium bicarbonate solution and brine. The organic layers were dried by anhydrous sodium sulfate, concentrated, and purified by preparative thin-layer chromotagraphy in 5% methanol/dichloromethane, giving 24 milligrams of the desired product.

Example 12

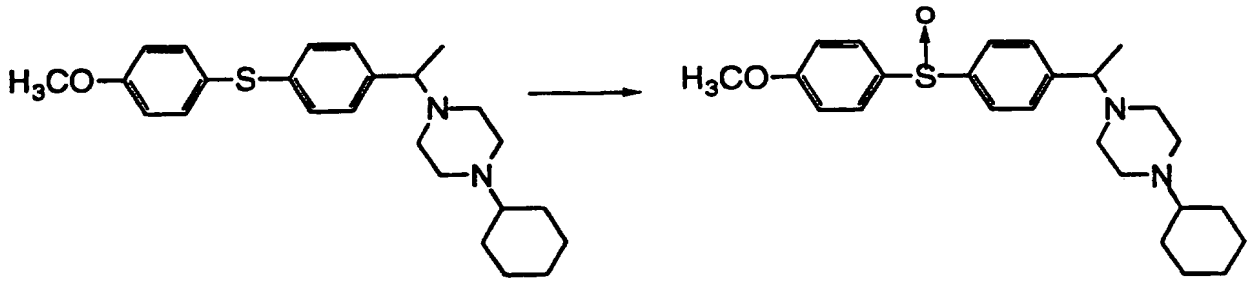
Alpha-alkylation of cyano compounds



200 milligrams (0.46 mm) of the starting nitrile were taken up under a nitrogen atmosphere in 10 mL of dry tetrahydrofuran at 0°. 1.2 mL (0.6 mm, 1.3 equivalents) of potassium hexamethyldisilazide solution (0.5 M in toluene) were added by syringe, and the resulting orange solution was stirred for ten minutes. 0.05 mL of iodomethane (1.3 equivalents) were added by syringe, which decolorized the solution. The reaction was stirred for 20 minutes while warming to room temperature, then diluted by the addition of 100 mL ethyl acetate, and extracted with saturated sodium bicarbonate solution and brine. The organic layers were dried by anhydrous sodium sulfate, concentrated, and purified by column chromatography in a gradient of hexane/ethyl acetate, giving 190 milligrams of the desired product (92% yield) as an oil that slowly solidified.

Example 13

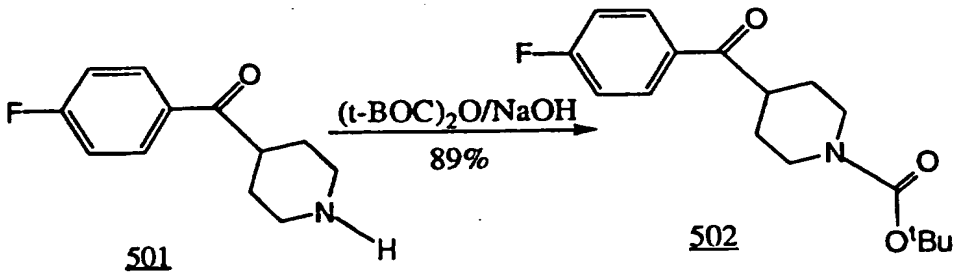
Oxidation of Sulfide to Sulfoxide



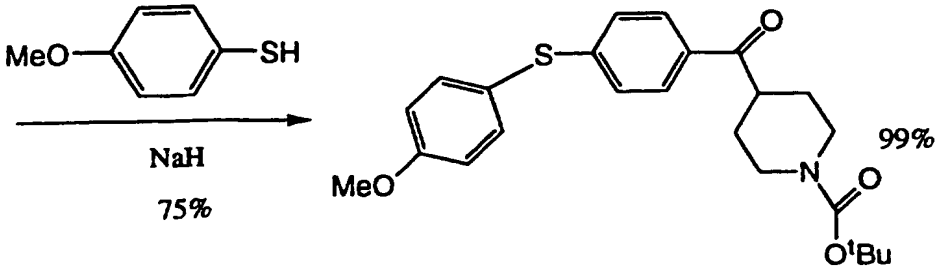
1.82 grams of the starting sulfide (4.4 mm) were dissolved in 20 mL of dichloromethane and 17 mL of a 0.5 N solution of methanesulfonic acid in dichloromethane. 1.15 grams of commercial MCPBA (60-80% pure) were added at 0°, and the solution was stirred for thirty minutes. The reaction mixture was diluted with ethyl acetate and extracted with saturated sodium bicarbonate. The organic layers were dried over sodium sulfate, concentrated, and purified by column chromatography in a gradient of 75% ethyl acetate/hexane to 5% methanol/ethyl acetate to give 1.22 grams of the desired sulfoxide and 0.4 grams of the corresponding sulfone.

Example 14

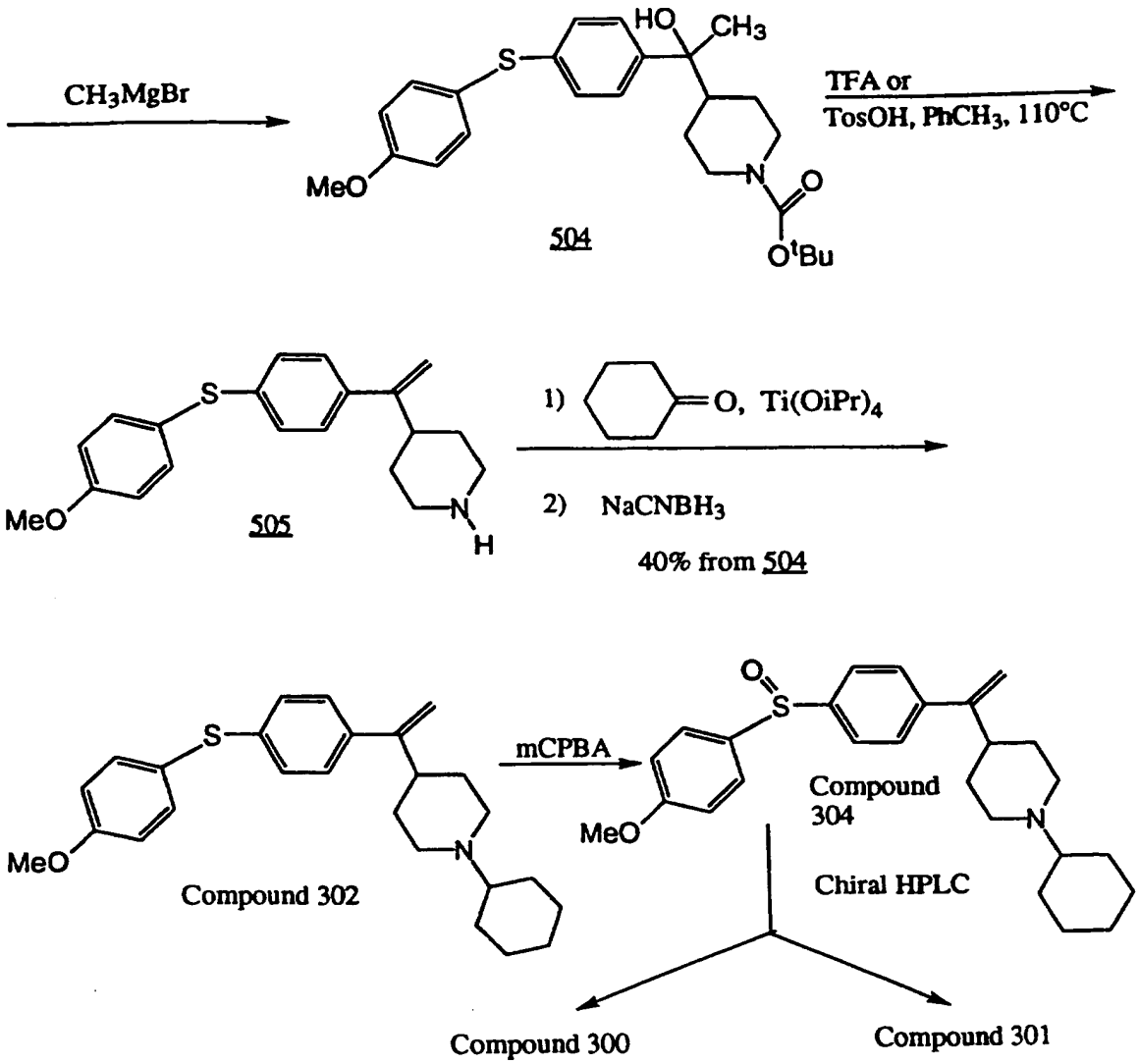
Synthesis of compounds 300, 301, 302, 304, and 760.



501 502



503


CH3MgBr
HO
CH3
S
MeO
N
O
O'Bu
504
TFA or
TosOH, PhCH3, 110°C
S
MeO
505
N
H
1) O, Ti(OiPr)4
2) NaCNBH3
40% from 504
S
MeO
Compound 302
mCPBA
O
S
MeO
Compound
304
N
Chiral HPLC
Compound 300
Compound 301

Step 1:

To a stirred mixture of 501 (5.0 g) in 50 ml of aqueous NaOH (20% w/w) was added, at 0°C, Di-tert-butyloxy dicarbonate (3.4 g, 1.2 eq.) dissovled in 50 ml of diethyl ether. The cooling bath was removed and the mixture was stirred at room temperature for 2 hours. Two phases were separated and the aqueous phase was extracted with 2x50 ml of ethyl acetate. The combined organic phases were dried over Na_2SO_4, filtered and concentrated to give a crude product. Purification by flash chromatography on silica gel (10% EtOAc-Hex.) afforded 3.5 g (89%) of 502 as a white solid (m.p. =89-90°C).

Step 2:

NaH (460 mg, 60% in mineral oil) was washed with dry hexanes and was stirred with 8 ml of dry DMF. To this mixtue was added 4-methoxythiophenol by syringe. The mixture was stirred at RT for 20 min. while the slurry became a clear solution. Compound 502 dissolved in 8 ml of DMF was added dropwise and the mixture was stirred at room temperature over night. Water (80 ml) was added and the mixture was extracted with 3x100 ml of EtOAc. The combined organic phases were dried over Na_2SO_4, filtered and concentrated to give a crude. Purification by flash chromatography on silica gel (20% EtOAc-Hex.) afforded 3.6 g (74%) of 503 as a white solid (m.p. = 105-107°C).

Step 3:

To a solution of 503 (1.5 g) in 40 ml of dry THF at 0°C, was added MeMgBr (1.15 ml, 3.0 M in ether). The mixture was stirred at 0°C for 1 h. and was quenched with 20 ml of a 10% $KHSO_4$. The aqueous phase was extracted with 2x50 ml of ethyl acetate. The combined organic phases were dried over Na_2SO_4,

filtered and concentrated to give a crude. Purification by flash chromatography on silica gel (30% EtOAc-Hex.) afforded 1.3 g (96%) of 504 as a solid, mp 129-130°.

Step 4:

At 0°C, 1.3g of 504 was dissolved in a mixture of 5 ml TFA and 15 ml CH_2Cl_2. The cooling bath was removed and the mixture was stirred at RT for 2h, quenched with saturated bicarbonate at 0°C, and the aqueous layer extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered and concentrated to give a white solid compound 505 which was used in the next step without further purification .

Step 5:

The white solid from step 4 was dissolved in 10 ml methylene chloride and to this solution was added 350 mg of cyclohexanone followed by 1.3 g of titanium (IV) isopropoxide. The mixture was stirred at RT over night. At 0°C, 440 mg of $NaCNBH_3$, dissolved in 2 ml of methanol was added and the mixture was stirred at RT for an additional 3 h. The mixture was quenched with water and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered and concentrated to give a crude product. Purification by flash chromatography on silica gel (100% EtOAc) afforded 0.5 g (40%) of Compound 302 as a white solid. The solid was dissolved in ethyl acetate, and treated with 2-3 equivalents of ethereal dry HCl. The mixture was evaporated to dryness in vacuo to give the hydrochloride, m.p. 227-30°.

Step 6:

To a stirred solution of 350 mg of compound 302 in 60 ml EtOAc and 60 ml CH_2Cl_2 were added 1.7 ml of $MeSO_3H$ (0.5 M in CH_2Cl_2), followed by 262 mg of

mCPBA (50-60%) at -40°C. The mixture was allowed to reach 0°C and was quenched with saturated bicarbonate solution (100 ml). The mixture was extracted with 3x100 ml of EtOAc. The combined organic phases were dried over Na_2SO_4, filtered and concentrated to give a crude product. Purification by flash chromatography on silica gel (15% EtOH-EtOAc) afforded 0.2 g (55%) of compound 304 as a white solid.

HPLC Separation of compound 304 on a Chiralcel OJ column; (Chiral Technologies, Inc., Exton, PA):

Compound 304 was separated on a 100-200 mg scale under the following conditions:

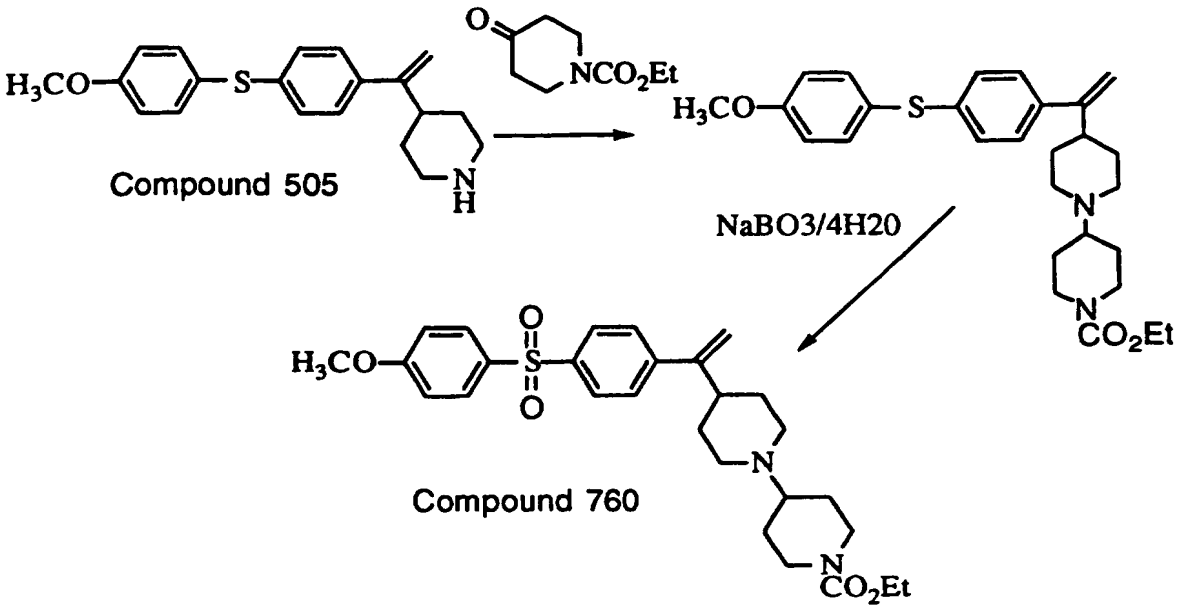
Solvent system: 0.1 % diethyl amine/3 % ethanol/hexane

Flow rate: 160 ml/min

Retention Time: 70 min for enantiomer A (compound 300, mp=141-142)

90 min for enantiomer B (compound 301, mp=141)

Synthesis of Compound 760:

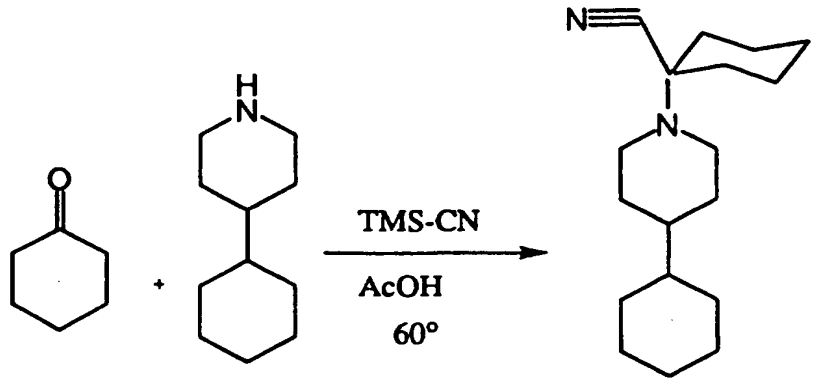


Compound 505 (0.375g, 1.15 mmol) and 4-carboethoxycyclohexanonone (0.294g, 1.72 mmol) were dissolved in 6 mL of CH_2Cl_2. The reaction mixture was then cooled to 0°C followed by addition of Ti(i-PrO)$_4$ (1.3 mL, 4.42 mmol). The reaction mixture was stirred at room temperature overnight, when TLC indicated there was no starting material. To the reaction mixture was slowly added a solution of $NaCNBH_3$ (0.364g, 5.8 mmol) in MeOH (2mL). The reaction mixture was then stirred at room temperature for 2h. The reaction was quenched by addition of 50 mL of 1N NaOH followed by 50mL of ethyl acetate. The reaction mixture was stirred at room temperature for 1 h then was extracted with ethyl acetate (50 mL x 3). The organic layer was dried with $NaHCO_3$. Solvent was removed and the residue was separated on a silica gel column (5% methanol/CH_2Cl_2) to afford the sulfide (0.46g, 83% yield) as an oil.

The sulfide (0.038g, 0.08 mmol) was dissolved in 2mL of HOAc followed by addition of $NaBO_3/4H_2O$ (0.037g, 0.24 mmol). The reaction mixture was stirred at room temperature overnight, when TLC indicated there was no starting material. To the reaction mixture was then added 1N NaOH until basic. The reaction mixture was extracted with ethyl acetate (20 mL x 3). The organic layer was dried with $NaHCO_3$. Solvent was removed and the residue was separated on a silica gel column (5% methanol/CH_2Cl_2) to afford Sch 65546 (0.007 mg, 17% yield) as an oil.

Example 15

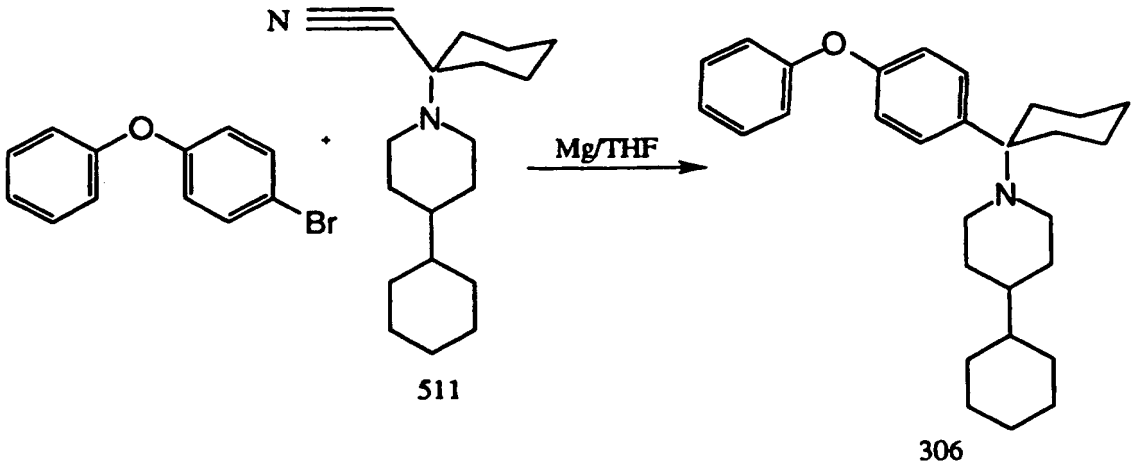
Synthesis of Compound 306.



511

Preparation of 511

To a solution of 25 mmol of cyclohexanone in 20 ml of acetic acid is added 62.5 mmol of cyclohexylpiperazine. The system is blanketed with N_2 and 31.3 mmol of TMS-cyanide, is added. The solution is then heated at 60°C under N_2 for approximately 20 hours. Acetic acid is removed on a rotary evaporator and the residue treated with 100 ml of water. This is extracted with EtOAc, (3X, 50 ml). Organic layers are washed with 100 ml. of water, dried with Na_2SO_4 and evaporated to give the crude product as an oil which is purified by column chromatograpy using 100:3:1 CH_2Cl_2:EtOH:NH_4OH as eluant. An oil was obtained, 10g of which was dissolved in 100ml CH_2Cl_2 and 50 ml water, then basified to pH 8 with K_2CO_3. The organic layer was dried with Na_2SO_4 and evaporated to obtain a light yellow powder, 6.6g.



511 306

Preparation of Compound 306:

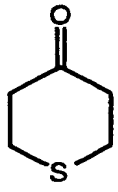
In a three necked round bottomed flask is placed 5.4 mmol of Mg and the flask is fitted with a condenser, dropping funnel and nitrogen inlet. The system is flame dried under nitrogen. Bromodiphenyylether (5.4 mmol), is dissolved in anhydrous THF, (10 ml), and added drop-wise. Addition of a drop of ethylene dibromide, iodine and occasional warming may be necessary to initiate Grignard formation. Once initiated the mixture is heated at reflux until all the Mg dissolves. Next, 1.8 mmol of cyanoamine 511 as a solution in 5 ml of dry THF is added, reflux is continued, and the reaction monitored by TLC.

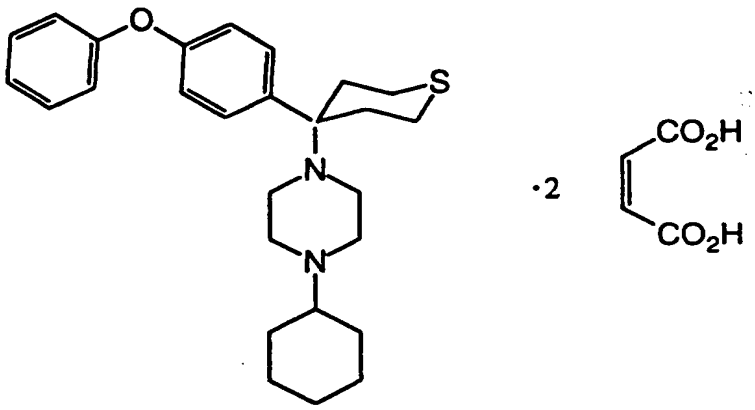
The reaction mixture is cooled to room temperature and quenched by addition of a saturated NH_4Cl solution, (10 ml). This is diluted with 10ml of water and extracted with 15 ml EtOAc, (3x). The organic extracts are dried with Na_2SO_4 and evaporated to give the crude product as an oil which is purified by column chromatography using ether/EtOAc as eluant. 370 ml of clear colorless oil was obtained.

The dimaleate salt was prepared by dissolving the oil in 10 ml of EtOAc and treating with 200 mg of maleic acid. A white powder was obtained (510 mg, mp = 144-146).

Example 16

Synthesis of Compound 303

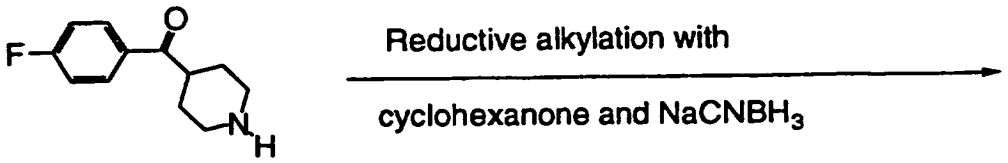
Example 15 is repeated except in place of cyclohexanone there is used a compound of the formula  . Compound 303 is obtained as a di-maleate:

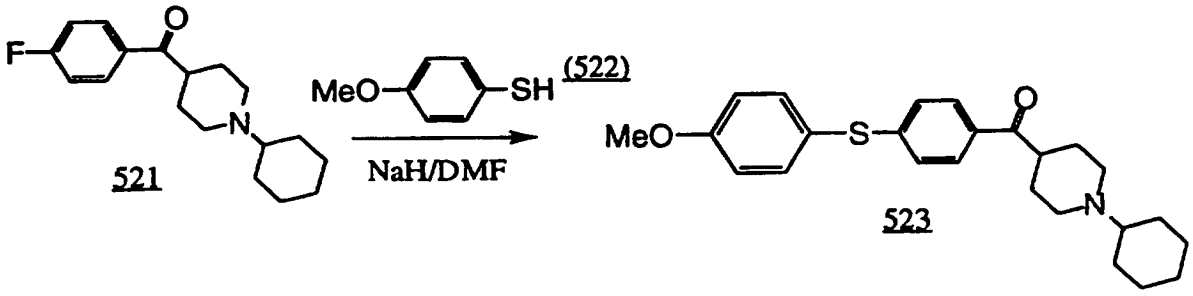


Compound 303

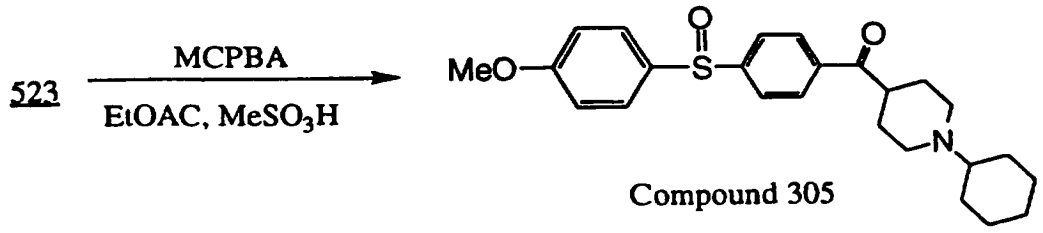
mp: 137-139

Example 17





NaH (334 mg,, 60% oil suspension) was washed with 15 ml of hexane, then stirred with 5 ml of DMF. Compound 522 (1.03 ml) was added without solvent, the mixture stirred at room temperature for 20 min, a solution of 521 (2.42g obtained by reductive alkylation) in 1.7 ml of hot DMF added, and the resulting mixture stirred at room termperature for two days. The mixture was quenched with water, and extracted with ethyl acetate. The extracts were purified by flash chromoatography over SiO_2 to give 3.0g of product 523, mp 128-9°.



m-Chloroperbenzoic acid (MCPBA, 81 mg) was added to a solution of 523 (105 mg) and $MeSO_3H$ (0.5 M in CH_2Cl_2, 1.0 ml) in 50 ml of ethyl acetate at -40°. Sufficient CH_2Cl_2 was added at this temperature to effect dissolution of solids,

and the mixture allowed to warm to room temperature. The mixture was quenched with excess $NaHCO_3$ solution, and extracted with ethyl acetate. The extracts were concentrated and purified by preparative thin-layer chromatography, developing with 20% ethanol-ethyl acetate to give Compound 305 N-oxide. This material was dissolved in CH_2Cl_2, CS_2 added, and the resulting mixture stirred for 3 hrs. at room temperature. Evaporation of volatiles and purification of the residue by preparative TLC as above gave Compound 305, mp 125°.

Example 18 (Process F)

Preparation of compounds 3-10 shown in Process F, where R is 4-methoxyphenyl, R3 and R4 are H, R1 is (S)-CH_3, and R27 is (R)-CH_3 and Preparation of Compound (3)

To an ice cooled solution of trifluoroacetic anhydride (19 mL) in CH_2Cl_2 (100 mL) add over 15 min (S)-(-)-α-methylbenzylamine (12.2 g) in CH_2Cl_2 (25 mL) with stirring, then stir at RT for 1h. Cool in ice and add methanesulfonic acid (40 mL) then powdered dibromodimethyl hydantoin (15 g). Stir till dissolved, then store for 20h at RT, protected from light. Add to a stirred solution of $NaHSO_3$ (5 g) in ice-H_2O (100mL), stir 5 min., separate, extract with CH_2Cl_2, wash the combined organics with H_2O and dry ($MgSO_4$). Filter on 30 g flash silica and elute with CH_2Cl_2 (300 mL). Evaporate the total eluates to dryness, add Et_2O (100 mL), stir 10 min. and add hexanes (500 mL). Stir 0.5h, filter, wash with hexanes and dry to obtain the 4-bromocompound (12.3 g) as white crystals.

Mp: 153-155°. Mass spectrum: MH^+ = 296/298.

Preparation of Compound (4)

Cool a solution of compound (3) (11.95 g) in dry THF (160 mL) to -70° under N_2 and add methyllithium (1.4M in Et_2O, 28.8 mL). Stir 5 min. then add n-butyllithium (2.5M in hexanes, 17 mL). Stir 5 min. then add 4-methoxybenzenesulfonyl fluoride (16 g). remove the cooling bath, stir for 0.5h, add 1N-HCl aq. (200 mL) and exteract with CH_2Cl_2. Wash with H_2O, dry ($MgSO_4$) and filter on a 15 g pad of flash silica gel, wash with 5% Et_2O-CH_2Cl_2 and

evaporate. Recrystallise with Et_2O-hexanes and dry to give the sulfone (13.4 g) as off-white crystals.

Mp: 97-100°. Mass specrtum: MH^+ = 388.

Preparation of Compound (5)

Reflux on a steam bath for 2h a mixture of compound (4) (17.5 g) and NaOH (6 g) in H_2O (15 mL) and ethanol (120 mL). Cool, add H_2O and extract with CH_2Cl_2 . Dry over K_2CO_3, filter and evaporate. Triturate with Et_2O-hexanes till solid, filter and dry to afford the amine (10.4 g), as a white solid.

Mp: 113-115°. Mass spectrum: MH+ = 292

Preparation of Compound (6)

To solution of compound (5) (1.46 g) in CH_2Cl_2 (20 mL) and potassium carbonate (2 g) in H_2O (10 mL) add ethyl (S)-lactate trifluoromethanesulfonate (1.1 g) and stir at RT for 5h. Wash with water, dry ($MgSO_4$), evaporate and chromatograph on flash silica gel, eluting with a 0-15% gradient of Et_2O in CH_2Cl_2. Evaporate the pure fractions and triturate in hexanes to obtain the crystalline ester (1.90 g)

Mp: 56-58°. Mass spectrum: MH+ = 392.

Preparation of Compound (7)

Reflux a mixture of compound (6) (1.73 g), acetonitrile (15 mL), anhydrous sodium carbonate (1.5 g) and ethyl iodoacetate (1.4 mL) for 48h., work up in H_2O-CH_2Cl_2, dry ($MgSO_4$) and evaporate. Chromatograph on silica, using a 0 to 10% gradient of Et_2O in CH_2Cl_2 and evaporate appropriate pure fractions to separately obtain the solid product (1.46 g) and recovered starting aminoester (0.53 g).

Mp: 69-71°. Mass spectrum: MH+ = 478.

Preparation of Compound (8)

Stir lithium aluminum hydride (0.45 g) in THF (15 mL) under N_2 with ice cooling and add over 2-3 min. a solution of diester (7) (1.30 g) in THF (25 mL). Stir in ice for 0.5h., add EtOAc (5 mL) dropwise, then add the solution to stirred, ice cooled 2N-NaOH solution (50 mL). Separate, extract the aq. with 3:1 Et_2O-CH_2Cl_2, combine, dry and evaporate the organics and triturate with a little Et_2O to obtain the diol as a white powder (0.88 g).

Mp: 123-125°. Mass spectrum: MH+ = 394.

Preparation of mixture (10)

Reflux a mixture of compound (8) (0.125 g), thionyl chloride (0.25 mL) and 1,2-dichloroethane (5 mL) for 1.5h., evaporate, co-evaporate with 3 mL dichloroethane and dry at high vacuum to obtain the mixture of dichlorocompounds as a pale yellow foam, suitable for use in the next step.

Preparation of compound numbers 730 and 803

These compounds are examples of compounds 11 and 12 as shown for process f.

Convert diol (0.125 g) to the dichlorides as described above, then reflux this product for 2h. in acetonitrile (2.5 mL) with *trans*-4-aminocyclohexanol hydrochloride (0.32 g), sodium iodide (0.5 g) and diisopropylethylamine (0.6 mL). Cool, and partition in H_2O-CH_2Cl_2. Dry and evaprorate the organic phase, and subject the residue to preparative TLC, eluting with acetone. Extract the separated bands with 1:1 CH_2Cl_2-MeOH, evaporate and dry at high vacuum to obtain the free bases as foams.

The less polar band (0.056 g) is compound no.730. Dissolve this in CH_2Cl_2 (2 mL) and add to stirred Et_2O (15 mL) containing 4M HCl-dioxan (0.4 mL). Centrifuge, wash by suspension-centrifugation in ether (2 x 15 mL) and dry under N_2 to obtain the dihydrochloride as a white powder.

Mp: 195-205°, with decomposition. Mass spectrum: MH+ = 473.

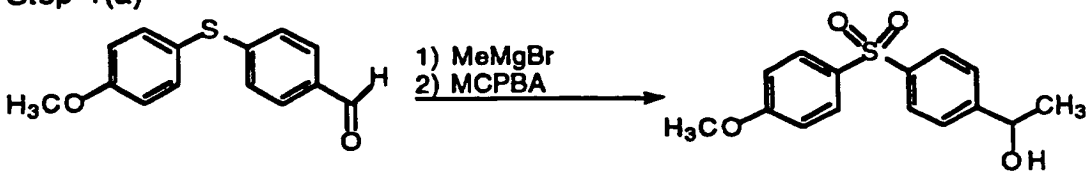
The more polar band (0.076 g) is compound 803. Convert this to the hydrochloride as above.

Mp: 215-225 C, with decomposition. Mass Spectrum MH+ =473

Example 19 (Process G)

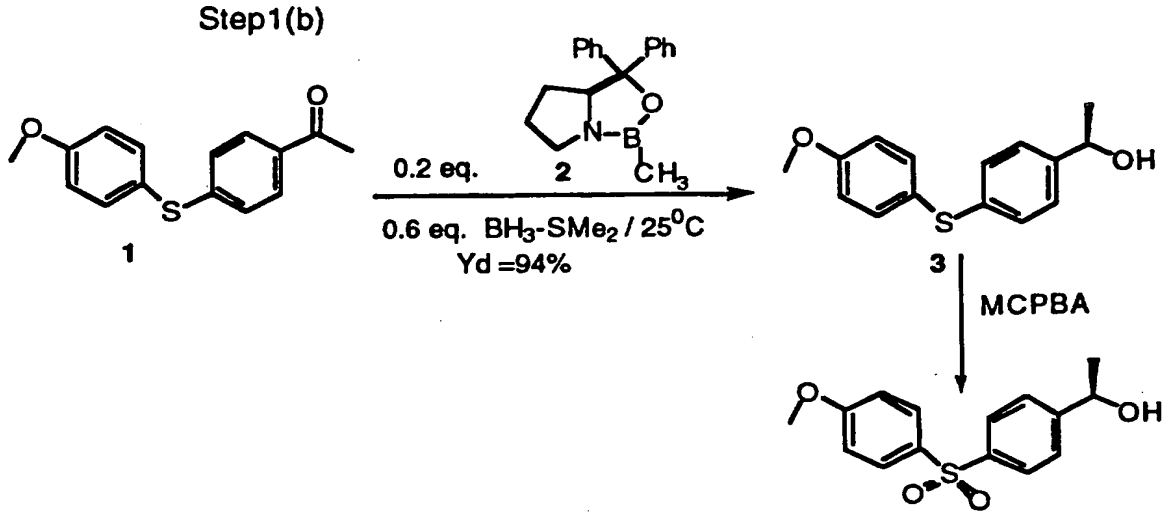
Preparation of compound 667 and 656

Step 1(a)



A solution of the aldehyde (Compound VII' of preparation 4, Process C, 4.9g, 0.02mol) in 50 mL THF was cooled in an ice water bath and methylmagnesium bromide (8.5mL, 3.0M) was slowly added. After 0.5h the temperature was warmed to room temperature where stirring was continued for 16h. After dilution with ethyl acetate and addition of water the organic layer was washed with water, brine, and concentrated. Drying under vacuum produced a yellow oil (5.1g) which was used without further purification.

A dichloromethane (150 mL) solution of the sulfide was cooled in an ice water bath where MCPBA (11.7g, 60%) was added. After stirring for 1h the temperature was warmed to room temperature and stirred for 16h. After diluting with ethyl acetate the reaction was washed with 10% sodium carbonate, water, and brine. The solution was concentrated and purified by chromatography with ethyl acetate to the sulfone alcohol.



To a clear pale yellow solution of the p-anisylthioacetophenone **1** (0.8g; 3.1 mmol) in anhydrous tetrahydrofuran (5mL) was added (S)-oxaborolidine catalyst **2** (0.168g; 0.6 mmol) and stirred at room temperature for 15 minutes. A solution of borane-methyl sulfide in tetrahydrofuran (2M from Aldrich Chemicals; 1.86 mmol; 0.93 mL) was added dropwise over 6 minutes to the solution of ketone **1** and catalyst **2** at room temperature. After 10 minutes of stirring, thin layer chromatography (TLC) showed absence of starting material and formation of a new, slightly more polar spot. The reaction was quenched by adding methanol (5mL) and stirring for 15 minutes. Volatiles were removed on the rotary evaporator and the residue was dissolved in methylene chloride (50 mL). The organic extract was washed with water, 1N.HCl, water, 10% $NaHCO_3$, brine and dried over magnesium sulfate. Concentration of the organic extract gave the carbinol **3** as a clear pale yellow oil (0.76g; yield=94%).

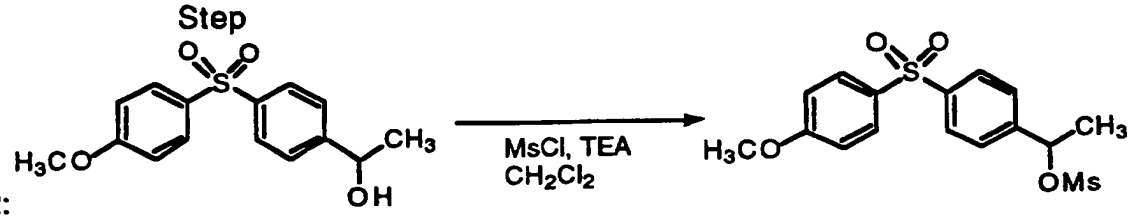
HPLC : AS-Column (5% i-PrOH in Hexanes); R_t ~ 19 min; R : S = 97:3 (94% ee / R-Alcohol)

$[\alpha]_D$ = + 26.1 (c= 0.1; $CHCl_3$)

A clear pale yellow solution of **3** (0.76g; 2.92 mmol) in anhydrous dichloroethane (8mL) at room temperature was treated sequentially with solid $NaHCO_3$ (0.6g; 7 mmol) and solid meta-chloroperoxybenzoic acid (1.1g; 6.43 mmol). The flask was fitted with a reflux condensor and the reaction mixture was heated to reflux. TLC at the end of 8 hours showed absence of **3** and formation of a more polar spot. Reaction mixture was allowed to cool to room teperature. The organic layer was decanted away from the white precipitate of

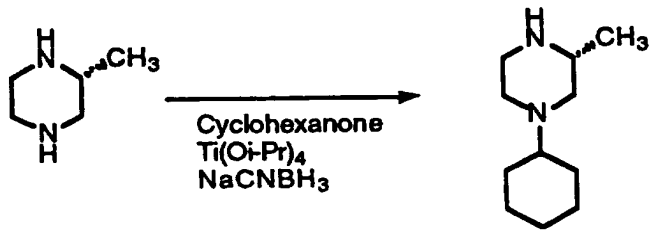
sodium salts, washing the solid residue with methylene chloride (2x20 mL). The combined organic extract was washed with water, 10% $Na_2S_2O_3$ solution, water, 10% $NaHCO_3$ solution and brine. Dried the organic layer over magnesium sulfate and concentrated to obtain ~0.8g of a pale yellow solid. Flash silicagel chromatography (20% EtOAc-CH_2Cl_2) gave 0.75g (88% from 1) of sulfone as a white solid, mp : 125-126^0 C $[\alpha]_D$ = + 22.1 (C = 0.095; $CHCl_3$)

Step 2:



To a suspension of the alcohol (4.0g, 13.6mmol) in dichloromethane (30mL) was added triethylamine (2.75g, 27.2mmol). The mixture was cooled in an ice/water bath and methanesulfonyl chloride (1.87g, 16.3mmol) was added dropwise. After 1h the mixture was diluted with dichloromethane and washed with water, 2% HCl, water, 10% $NaHCO_3$ and brine. After drying over sodium sulfate the solvent was evaporated to afford the crude product as a gum. It was used without further purification.

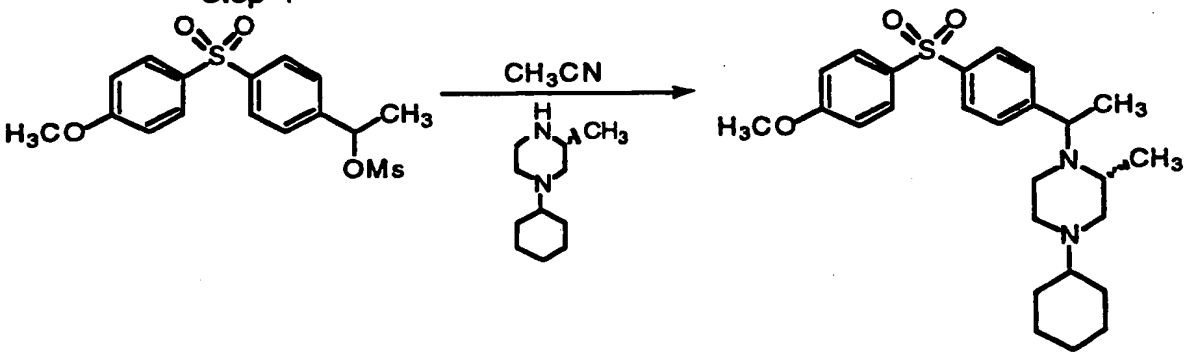
Step 3:



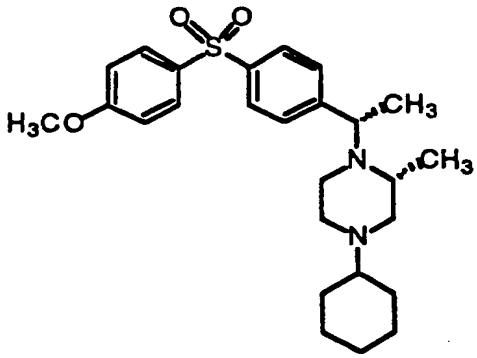
2-(R)-Methylpiperazine (30g, 0.3 mol) and cyclohexanone (32g, 0.33mol) were dissolved in methylene chloride (60mL) and cooled in an ice/water bath where titanium (IV) isopropoxide (93g, 0.33mol) was added dropwise. Stirring was continued for 1h at 0^o C then at room temperature for 16h. A solution of sodium cyanoborohydride (21g, 0.33mol) in methanol (200mL) was added with stirring continued for 24h. The mixture was diluted with 1L ethyl acetate and stirred with 400mL 10% NaOH for 1h. The aqueous solution containing a white precipitate was discarded. The organic layer was washed with

water and brine, followed by concentration on a rotary evaporator. The residue purified by flash chromatography with 25:1 CH_2Cl_2 / MeOH (saturated with aqueous ammonia), yield = 50%.

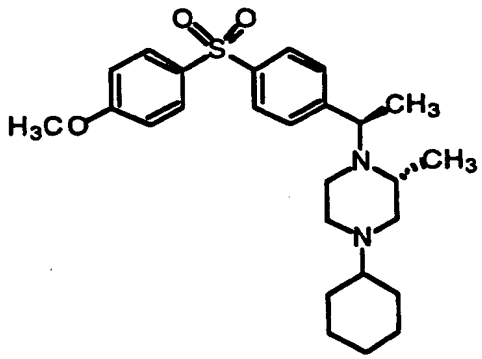
Step 4



The mesylate from step 2 (4.8g, 13mmol) and 1-cyclohexyl-3(R)-methylpiperazine (3.5g, 19.4mmol) were dissolved in 40mL CH_3CN and heated to 60 C where stirring was continued for 24h, then refluxed for 8h. The solvent was removed and the residue dissolved in ethyl acetate. The organic layer was washed with 10% sodium carbonate and brine. The solvent was evaporated and the residue chromatographed with 4:1 dichloromethane/acetone. When step 1a is used, two diastereomers (compounds 656 and 667) were collected in a 1:1 ratio (656: R_f 0.40, ethyl acetate: Anal. calc. C 68.39, H 7.95, N 6.13, S 7.02; found C 68.01, H 8.02, N 6.09, S 7.05. 667: R_f 0.30, ethyl acetate: found C 68.06, H 8.08, N 6.18, S 6.84). When step 1b is used starting with the (S)-oxaborolidine shown, then the product is 656 while (R)-oxaborolidine catalyst gives 667.



Compound 656
Isomer A

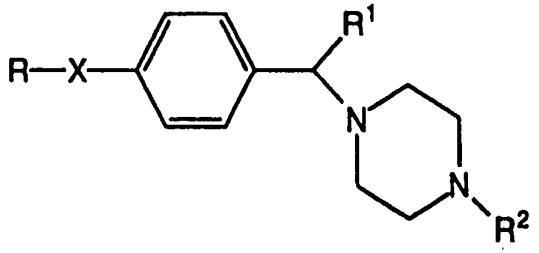


Compound 667
Isomer B

By appropriate choice of starting materials, the following compounds were prepared. In these tables the following notes apply.

t-BOC means t-butloxycarbonyl. The compound numbering is not consecutive. A (+) or (-) after a compound number indicates the optical rotation of the stereoisomer for which data is given. "IsoA" or "IsoB" after a compound number indicates an assignment of A or B to different stereoisomers of a compound having the same structural formulas without regard to optical rotation. When the chiral atom has been identified, "isoA" or isoB" is listed after a substituent for that atom. NBA is nitrobenzyl alcohol, G/TG is glycerol/thioglycerol. Chex means cyclohexyl.

Compounds having the formula



#	R	X	R^1	R^2	Mass Spectrum or MP
1	C_6H_5	S	CH_3	CH_3	MP = 254-256 (di-HCl)
2	C_6H_5	SO_2	CH_3	CH_3	MP=226-230 (di-HCl)
3	C_6H_5	SO	CH_3	CH_3	MP=240-242 (di-HCl)
4	C_6H_5	SO	CH_3	H	MP=80-85 (dimaleate)
5	C_6H_5	S	CH_3	H	MP=227-229 (di-HCl)
6	C_6H_5	SO_2	CH_3	H	MP=180-220 (di-HCl hydrate)
7	C_6H_5	SO_2	CH_3	$(CH_2)_2OH$	MP=236-238 (di-HCl)
8	4-Cl-C_6H_4	SO_2	CH_3	$(CH_2)_2OH$	MP=242-244 (di-HCl)
9	C_6H_5	O	CH_3	$(CH_2)_2OH$	CI(CH_4):327(M+1), 309, 197
10 (+)	C_6H_5	SO_2	CH_3	$(CH_2)_2OH$	FAB -NBA-G/TG-DMSO: 375(M+1)
11(-)	C_6H_5	SO_2	CH_3	$(CH_2)_2OH$	FAB-NBA-G/TG-DMSO: 375(M+1)
12	2-pyridyl	O	CH_3	CH_3	MP = 172-175 (Dimaleate)
13	C_6H_5	O	CH_3	$(CH_2)_2O(CH_2)_2OH$	EI: 370 (M+), 197, 99
14	C_6H_5	SO_2	i-Pr	$(CH_2)_2OH$	EI: (M+1)402, 359, 329, 128,
15	C_6H_5	SO_2	CH_3	2-CH_3O-C_6H_4	FAB-NBA-G/TG-DMSO: 437 (M+1)
16	C_6H_5	SO_2	CH_3	cyclohexyl	CI(CH_4): (m+1) 413
17	C_6H_5	SO_2	i-Pr	cyclohexyl	CI(CH_4): (M+1) 441, 397, 299
18	4-$CH_3C_6H_4$	SO_2	CH_3	cyclohexyl	EI: 427(M+1), 383, 167
19	C_6H_5	SO_2	CH_3	C_6H_5	SIMS-NBA-G/TG-DMSO: 407 (M+1), 232
20	3-pyridyl	O	CH_3	$(CH_2)_2OH$	MP = 165-168 (Dimaleate)

21	3-pyridyl	O	CH_3	cyclohexyl	MP = 219-222 (Dimaleate)
22	3-pyridyl	S	CH_3	$(CH_2)_2OH$	MP = 155-158 (Dimaleate)
23	3-pyridyl	S	CH_3	cyclohexyl	MP = 157-159 (Dimaleate)
24	2-CH_3-4-pyridyl	O	CH_3	$(CH_2)_2OH$	MP = 165-166 (Dimaleate)
25	2-CH_3-4-pyridyl	O	CH_3	cyclohexyl	MP = 90-91
26	C_6H_5	O	CH_3	cyclohexyl	EI: 364 (M+), 349, 197, 167
27	C_6H_5	SO_2	C_6H_5	cyclohexyl	FAB-NBA-G/TG-DMSO: (M+1) 475, 335, 307, 257
28	C_6H_5	SO_2	i-Pr	$(CH_2)_3OH$	FAB-G/TG-DMSO: (M+1) 417, 373, 315, 273
29	C_6H_5	SO_2	i-Pr	$(CH_2)_2O(CH_2)_2OH$	FAB-NBA-G/TG-DMSO: (M+1) 447, 404, 329, 315
30	C_6H_5	SO_2	n-Bu	cyclohexyl	MP = 217-220
31	4-Cl-C_6H_4	SO_2	i-Pr	cyclohexyl	MP = 134-137 (dec)
32	4-CH_3-C_6H_4	SO_2	i-Pr	cyclohexyl	MP = 208-210
33	C_6H_5	SO_2	CH_3	4-NO_2-C_6H_4	FAB-NBA-G/TG-DMSO: 452(M+1)
34	C_6H_5	SO_2	CH_3	$(CH_2)_3OH$	FAB-NBA-G/TG-DMSO: 389(M+1)
35	4-CH_3-C_6H_4	SO_2	CH_3	2,3-$(CH_3)_2$-C_6H_3	CI(CH_4): 449(M+1), 191, 148
36	4-Cl-C_6H_4	SO_2	CH_3	cyclohexyl	FAB-NBA-G/TG-DMSO: 447(M+1)
37	3-pyridyl	O	i-Pr	cyclohexyl	MP = 150-153 (Difumarate)
38	4(CH_3O)C_6H_4	SO_2	i-Pr	cyclohexyl	CI(CH_4):(M+1)471, 427, 305, 289, 144,
39	4-Cl-C_6H_4	SO_2	C_6H_5	cyclohexyl	FAB-NBA-G/TG-DMSO:510 (M+1), 399, 341
40	4-Cl-C_6H_4	SO_2	n-Bu	cyclohexyl	FAB-NBA-G/TG-DMSO: 489 (M+1), 349, 314
41	4-(t-Bu)C_6H_4	SO_2	i-Pr	cyclohexyl	FAB-NBA-G/TG-DMSO: 497 (M+1), 453, 371, 329, 301, 223
42	3-Cl-C_6H_4	SO_2	CH_3	cyclohexyl	CI(CH_4): 447 (M+1)

43	C_6H_5	SO_2	cyclohexyl	cyclohexyl	CI(CH_4): 481 (M+1), 341, 315, 219, 169, 167, 111, 79
44	C_6H_5	SO_2	CN	cyclohexyl	CI(CH_4): 424 (M+1), 397, 328, 286, 258, 233, 197, 169, 167, 111, 79
45	C_6H_5	O	CH_3	$(CH_2)_2$-O-t-BOC	FAB-SIMS-NBA-G/TG-DMSO: 411 (M+1), 308, 197
46 (+)	4-CH_3-C_6H_4	SO_2	CH_3	cyclohexyl	EI:427 (m + 1), 388, 167
47(-)	4-CH_3-C_6H_4	SO_2	CH_3	cyclohexyl	EI:427 (m + 1), 388, 167
48	C_6H_5	O	CH_3	$(CH_2)_3$-O-t-BOC	CI(Isobutane): 425 (M+1)
49	4-t-Bu-C_6H_4	SO_2	CH_3	cyclohexyl	CI(CH_4): (M+1) 469, 456
50	4(CH_3O)C_6H_4	SO_2	CH_3	cyclohexyl	CI(CH_4): (M+1) 443, 399, 167, 125
51	4-CH_3-C_6H_4	SO_2	CN	cyclohexyl	CI(Isobutane): 438(M+1), 411, 272, 261, 169
52	2,4-$(Cl)_2$-C_6H_3	O	CH_3	cyclohexyl	CI(Isobutane): 435(M+2), 434, 433, 314, 312, 267, 265, 195, 169, 167
53	4-CH_3-C_6H_4	SO_2	CH_3	$(CH_2)_2NHCOCH_3$	CI (CH_4): 430 (M+1), 357
54	4-t-Bu-C_6H_4	O	CH_3	cyclohexyl	CI(Isobutane): 421 (M+1) 349. 335, 261, 259, 91
55	n-Bu	O	CH_3	cyclohexyl	CI(Isobutane): 345 (M+1), 177, 169
56	4-CH_3-C_6H_4	SO_2	CH_3	CH_2CONH_2	CI(CH_4): 402 (M+1)
57	2-pyrimidyl	O	CH_3	cyclohexyl	MP = 191-193 (Dimaleate)
58	4-CH_3-3-pyridyl	O	CH_3	cyclohexyl	MP = 168-170 (Dimaleate)
59	4-CH_3-C_6H_4	SO_2	CH_3	CH_2-cyclohexyl	CI (CH_4): 441 (M+1)
60	3-pyridyl	O	CH_3	CH_2-cyclohexyl	MP = 187-189 (Dimaleate)
61	2-benzoxazolyl	O	CH_3	cyclohexyl	MP = 165-168 (Maleate)
62	3-pyridyl	O	CH_3	$CH_2CH(OH)C_6H_5$	MP = 162-164 (Dimaleate)
63	3-pyridyl	O	CH_3	bicyclo[2.2.1]hept-2-yl	MP = 168-175 (Dimaleate)
64	C_6H_5	O	CH_3	$(CH_2)_2OCOCH_2$-tBu	CI(CH_4): 425 (M+1), 309, 197
65	1-Me-2-imidazolyl	S	CH_3	cyclohexyl	MP = 155-158 (Dimaleate)
66	2-pyrimidyl	O	CH_3	cyclopentyl	MP = 178-181 (Dimaleate)
67	2-pyrimidyl	O	CH_3	cycloheptyl	MP = 167-171 (Dimaleate)
68	2-pyrimidyl	O	CH_3	tetrahydrothiapyran-4-yl	MP = 157-160 (Dimaleate)

69	2-pyrimidyl	O	CH_3	3-Me-2-butenyl	MP = 180-182 (Dimaleate)
70	2-pyrimidyl	O	CH_3	2-cyclohexenyl	MP = 171-174 (Dimaleate)
71	2,4-$(MeO)_2$-6-pyrimidyl	O	CH_3	cyclohexyl	MP = 196-199 (Dimaleate)
72	4-CF_3-2-pyridyl	O	CH_3	cyclohexyl	MP = 178-182 (Dimaleate)
73	3-Me-2-butenyl	O	CH_3	cyclohexyl	MP = 194-197 Dimaleate)
74	2-pyrimidyl	S	CH_3	cyclohexyl	MP = 182-184 (Dimaleate)
75	4-Me-2-pyrimidyl	S	CH_3	cyclohexyl	MP = 163-165 (Dimaleate)
76	3-pyridyl	O	CH_3	1-azabicyclo[2.2.2]-oct-3-yl	MP = 182-184
77	3,4-$(MeO)_2$-C_6H_3	SO_2	CH_3	cyclohexyl	SIMS-NBA-G/TG-DMSO: 473 (M+1), 399, 337, 305, 273, 214
78	4-Me-2-pyrimidyl	O	CH_3	cyclohexyl	MP = 179-181 (Dimaleate)
79	4-HO-C_6H_4	O	CH_3	cyclohexyl	CI(CH_4):(M+1) 381, 287, 241, 213, 195, 167,
80	4-Et-C_6H_4	O	CH_3	cyclohexyl	CI(CH_4):(M+1)393, 377, 253, 225, 195, 169,
81	1-piperidyl	CH_2	CH_3	cyclohexyl	CI(Isobutane):(M+1) 370,
83	4-CH_3-C_6H_4	SO_2	CH_3	2-ketocyclohexyl	CI(CH_4): 441(M+1), 345, 261
84	4-CH_3-C_6H_4	SO_2	CH_3	$(CH_2)_2OH$	SIMS-NBA-G/TG-DMSO: 389 (M+1)
85	3,5-$(CH_3)_2$-C_6H_3	O	CH_3	cyclohexyl	EI:(M+1) 392, 377, 343, 327, 225, 155,
86	4-CH_3O-C_6H_4	O	CH_3	cyclohexyl	CI(Isobutane): 395 (M+1), 269, 227, 181, 169
87	2-cyclohexenyl	O	CH_3	cyclohexyl	CI(Isobutane): 369 (M+1), 288
88	4-Cl-2-pyrimidyl	O	CH_3	cyclohexyl	MP = 160-161 (Dimaleate)
89	4,6-$(Cl)_2$-2-pyrimidyl	O	CH_3	cyclohexyl	MP = 180-182.5 (Dimaleate)
90	2,4-$(MeO)_2$-1,3,5-triazin-6-yl	O	CH_3	cyclohexyl	MP = 198-200 (Dimaleate)
91(-)	2-pyrimidyl	O	CH_3	cyclohexyl	CI(CH_4): 367 (M+1), 199,142
92 (+)	3-Cl-C_6H_4	SO_2	CH_3	cyclohexyl	CI(CH_4): 449, 447 (M+1),

93 (-)	3-Cl-C_6H_4	SO_2	CH_3	cyclohexyl	Cl(CH_4): 449, 447 (M+1),
94 (+)	2-pyrimidyl	O	CH_3	cyclohexyl	Cl(CH_4): 367 (M+1), 199, 142
95	tetrahydropyran-4-yl	O	CH_3	cyclohexyl	MP = 218 - 220 (diHCl)
96	2,3,5-$(Me)_3$-C_6H_2	O	CH_3	cyclohexyl	EI(M+1):406, 266, 239, 167
97	4-CH_3-C_6H_4	SO_2	CH_3	1-methylbutyl	SIMS-NBA-G/TG-DMSO: 415 (M+1)
98	C_6H_5	S	CH_3	cyclohexyl	Cl(CH_4): 381(M+1)
99	6-Cl-3-pyridazinyl	O	CH_3	cyclohexyl	MP = 115-117
100	6-MeO-3-pyridazinyl	O	CH_3	cyclohexyl	MP = 123-127
101	3-pyridazinyl	O	CH_3	cyclohexyl	MP = 113-115
102	2-MeS-4-pyrimidinyl	O	CH_3	cyclohexyl	MP = 185-187 (Dimaleate)
103	2-thiazolyl	O	CH_3	cyclohexyl	MP = 184-186 (Dimaleate)
104	pivaloyl	O	CH_3	cyclohexyl	Cl(CH_4): 373 (M+1), 205, 169, 167, 121
106	4-CH_3O-C_6H_4	S	CH_3	cyclohexyl	Cl(Isobutane): (M+1) 411, 243, 169,
107	3,4-$(MeO)_2C_6H_3$	S	CH_3	cyclohexyl	Cl(CH_4):(M+1) 441, 273, 164,
108	C_6H_5	C(CH_3)(OH)	CH_3	cyclohexyl	MP = 185-18 Dimaleate
109	N-morpholinyl	CH_2	CH_3	cyclohexyl	Cl(CH_4): 372 (M+1), 285, 249, 204, 191, 169, 167, 119
110	4-Me-piperazin-1-yl	CH_2	CH_3	cyclohexyl	Cl(CH_4):385(M+1),217, 195, 169, 113, 89
111	C_6H_5	C=CH_2	CH_3	cyclohexyl	MP = 189-191 (Dimaleate)
112	C_6H_5	CHOH	CH_3	cyclohexyl	Cl(CH_4):379 (M+1), 362, 301, 273, 211, 195, 169, 166
113	pyrazinyl	O	CH_3	cyclohexyl	MP = 110-111
114	2-propynyl	O	CH_3	cyclohexyl	MP = 173-175 (Dimaleate)
115	2-hydroxyethyl	O	CH_3	cyclohexyl	Cl(CH_4): (M+1) 333, 317, 205, 165, 121
116	benzyl	O	CH_3	cyclohexyl	EI:(M+1) 470, 455, 330, 303, 167
117	H	CO	CH_3	cyclohexyl	Cl(CH_4):301 (M+1), 385, 195, 169, 135, 119

118	CH_3	CO	CH_3	cyclohexyl	MP = 158-161 (dimaleate)
119	4-CH_3O-C_6H_4	CHOH	CH_3	cyclohexyl	EI: 408, 279, 268, 241, 167, 135, 126.
120	$(Me)_2NCO$	O	CH_3	cyclohexyl	CI(CH_4):(M+1) 360, 273, 220, 192, 108
121	4-NO_2-C_6H_4	O	CH_3	cyclohexyl	SIMS-NBA-G/TG-DMSO:409 (M+1), 393, 366, 338, 283, 270, 242, 196, 167
122	4-HO-C_6H_4	S	CH_3	cyclohexyl	CI(CH_4):(M+1) 397, 257, 229, 195, 167
123	4-CH_3O-C_6H_4	SO	CH_3	cyclohexyl	SIMS-NBA-G/TG-DMSO:427.2 (M+1), 343
124	C_6H_5	CH=CH	CH_3	cyclohexyl	MP = 108-111
125	4-CH_3O-C_6H_4	CO	CH_3	cyclohexyl	CI(CH_4): 407 (M+1), 299, 269, 241, 197, 169, 167, 135.
126	3-CH_3O-C_6H_4	S	CH_3	cyclohexyl	CI(CH_4): 411, (M+1), 271, 245, 243, 195, 169, 166.
127	4-Br-2,3,5,6-tetrafluoro-phenyl	O	CH_3	cyclohexyl	CI(CH_4):515 (M+1), 437, 435, 271, 269, 191, 167.
128	3-CH_3O-C_6H_4	SO	CH_3	cyclohexyl	MP = 231 - 234
129	4-CHO-C_6H_5	O	CH_3	cyclohexyl	SIMS-NBA-G/TG-DMSO:393 (M+1), 365, 307, 289,273, 262, 257, 246, 225
130	4-HO-C_6H_5	SO	CH_3	cyclohexyl	CI(CH_4):(M+1) 413, 397, 271, 229, 167
131	3,4-$(CH_3O)_2C_6H_4$	SO	CH_3	cyclohexyl	CI(Isobutane): (M+1) 457,441,
132	3-phenyl-2-propynyl	O	CH_3	cyclohexyl	MP = 191-194 (Dimaleate)
133	3-phenyl-2-propenyl	O	CH_3	cyclohexyl	MP=145-148 (HCl)
134	2-butynyl	O	CH_3	cyclohexyl	MP = 190-192 (dimaleate)
135	4-CH_3O-C_6H_4	SO_2	CN	cyclohexyl	SIMS-NBA-G/TG DMSO 454: (M+1), 427, 399, 346, 299, 274, 257, 238, 215
136	2-pyrimidinyl	SO_2	CH_3	cyclohexyl	MP = 194-195 (dimaleate)
137	2-pyrimidinyl	SO	CH_3	cyclohexyl	MP = 165-167 (dimaleate)
138	3-pyridyl	SO	CH_3	cyclohexyl	MP = 123-125
139	3-pyridyl	SO_2	CH_3	cyclohexyl	MP = 142-145

140	3-CH_3O-C_6H_4	O	CH_3	cyclohexyl	SIMS-NBA-G/TG-DMSO: 395.4 (M+1), 258, 238, 227,
142	4-CH_3O-C_6H_4	C=NOH ISO 1	CH_3	cyclohexyl	EI:(M+1) 421, 405, 378, 265, 239,
143	4-CH_3O-C_6H_4	C=NOH ISO 2	CH_3	cyclohexyl	EI:(M+1) 421, 405, 377, 265, 254
144	4-CH_3O-C_6H_4	S	CN	cyclohexyl	SIMS-NBA-G/TG-DMSO: 422 (M+1), 395, 300, 273, 257, 254, 238
145	4-CH_3O-C_6H_4	SO	CN	cyclohexyl	CI(CH_4):438.2(M+1), 411.3, 331, 254.2
146	benzyl	C≡C	CH_3	cyclohexyl	MP = 180-183 (dimaleate)
147	1-Me-1-propynyl	O	CH_3	cyclohexyl	MP = 174-176 (dimaleate)
148	4-CH_3O-C_6H_4	C=NOCH_3	CH_3	cyclohexyl	CI(Isobutane):(M+1) 436, 404,
150	2-(CH_3O)C_6H_4	CHOH	CH_3	cyclohexyl	EI:(M+1) 408, 393, 282, 241, 167
151	2-thienyl	C(CH_3)(OH)	CH_3	cyclohexyl	MP = 147-149
152	4(CF_3O)C_6H_4	SO_2	CH_3	cyclohexyl	SIMS-NBA-G/TG-DMSO: 497 (M+1), 481, 413, 329, 257, 238
153	2(CH_3O)C_6H_4	CO	CH_3	cyclohexyl	FAB(+ve)-HMR: (M+1) 407, 397, 329, 307, 260, 237,
154	$CH_3COOC_6H_4$	S	CH_3	cyclohexyl	EI:(M+1) 438, 395, 298, 271, 229, 167,
155	4-CH_3SO_2-C_6H_4	SO_2	CH_3	cyclohexyl	FAB(+ve)-HMR: (M+1) 491, 475, 391, 365, 273, 257
156	C_6H_5	SO iso A	CH_3	cyclohexyl	CI(CH_4):397 (M+1), 382, 213, 167
158	C_6H_5	SO iso B	CH_3	cyclohexyl	CI(CH_4):397 (M+1), 382, 213, 167
159	2-pentynyl	O	CH_3	cyclohexyl	191-193 (dimaleate)
160	2-thienyl	C=CH_2	CH_3	cyclohexyl	MP = 173-176 (dimaleate)
161	C_6H_5	O	CH_3	$(CH_2)_2OCOC(Me)_2$ n-C_3H_7	CI(CH_4): 439(M+1)
162	3-butenoyl	NH	CH_3	cyclohexyl	MP = 155-156

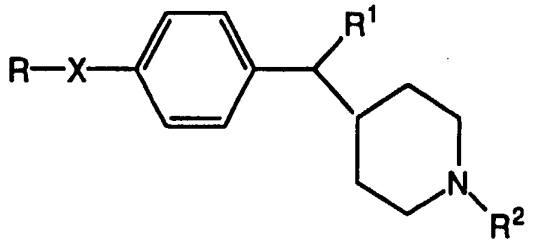
163	$4(CH_3O)C_6H_4$	CH_2	CH_3	cyclohexyl	CI(Isobutane):393 (M+1), 379, 285, 225, 169
164	3-(3,4-methylenedioxy-phenyl)-2-propenoyl	NH	CH_3	cyclohexyl	SIMS-NBA-G/TG-DMSO: 462 (M+1), 294, 174, 169, 120
165	trifluoroacetyl	NH	CH_3	cyclohexyl	MP = 127-130
166	CH_3	C=N-O-2-pyrimidyl	CH_3	cyclohexyl	MP = 173-174 (dimaleate)
167	$4(CH_3S)C_6H_4$	S	CH_3	cyclohexyl	$CI(CH_4)$:(M+1) 427, 303, 259, 195, 167,
168	$4(CH_3)C_6H_4$	SO_2	CH_3	$(CH_2)_3N(Et)COC(Me)_2$ $n\text{-}C_3H_7$	$CI(CH_4)$: 514 (M+1)
169	$4(CH_3O)C_6H_4$	SO IsoA	CN	cyclohexyl	SIMS-NBA-G/TG-DMSO: 438 (M+1), 411, 395, 331, 254, 246, 214
170	$4\text{-}CH_3SO_2\text{-}C_6H_4$	SO	CH_3	cyclohexyl	CI(Isobutane):(M+1)475,459
171	$4\text{-}CH_3SO\text{-}C_6H_4$	SO	CH_3	cyclohexyl	FAB(+ve)-HMR:(M+1) 458, 443, 365, 307, 273, 257
172	p-toluenesulfonyl	NH	CH_3	cyclohexyl	EI: 441, 301, 273, 167, 118
173	methanesulfonyl	NH	CH_3	cyclohexyl	CI (CH_4): 399 (M+1),260,169
174	2-propynyl	NH	CH_3	cyclohexyl	CI (CH_4): 326 (M+1), 195, 158
175	2-pyrimidinyl	S	CN	cyclohexyl	$CI(CH_4)$: 394 (M+1), 367, 257, 217, 167.
176	4-Me-1-piperazinyl	SO_2	CH_3	cyclohexyl	$CI(CH_4)$: 435 (M+1), 269, 217, 183, 170, 167.
177	$4(CH_3O)C_6H_4$	SO Iso B	CN Iso B	cyclohexyl	SIMS-NBA-G/TG-DMSO: 438(M+1), 411, 395, 331, 254, 246, 214
178	C_6H_4	SO ISO B	CN	cyclohexyl	CI(Isobutane): (M+1) 408, 381, 233, 169
179	2-pyrimidinyl	SO	CN	cyclohexyl	SIMS -NBA-G/TG-DMSO) 410 (M+1), 383, 331, 307
180	1-piperidyl	SO_2	CH_3	cyclohexyl	CI(Isobutane): 420 (M+1), 376, 188, 167, 140, 125, 112, 85

181	N-morpholino	SO_2	CH_3	cyclohexyl	CI(Isobutane): 372, (m + 1) 370, 285, 249, 204, 191, 170, 167, 119, 100, 88
182	2-thiazolyl	S	CH_3	cyclohexyl	178-180 (dimaleate)
183	2-thiazolyl	SO	CH_3	cyclohexyl	MP = 179-180 (dimaleate)
184	6-Cl-3-pyridazinyl	S	CH_3	cyclohexyl	MP = 123-125
185	6-Cl-3-pyridazinyl	SO_2	CH_3	cyclohexyl	MP = 154-156
186	6-Cl-3-pyridazinyl	SO	CH_3	cyclohexyl	MP = 135-137
187	4-$(CH_3SO)C_6H_4$	S	CH_3	cyclohexyl	FAB(+ve)-HMR: (M+1) 433, 427, 275, 259, 169,
188	t-BOCNH$(CH_2)_7$CO	NH	CH_3	cyclohexyl	SIMS-NBA-G/TG-DMSO: 529 (M+1), 261
189	4$(CH_3O)C_6H_4$	S	CH_2NH_2	cyclohexyl	CI(Isobutane): (M+1) 426, 395,
190	propadienyl	S	CH_3	cyclohexyl	MP = 175-177 (dimaleate)
191	propadienyl	SO_2	CH_3	cyclohexyl	MP = 143-145 (dimaleate)
192	propadienyl	SO	CH_3	cyclohexyl	MP = 159-161 (dimaleate)
193	2-propynyl	SO	CH_3	cyclohexyl	MP = 153-156 (dimaleate)
194	1-propynyl	S	CH_3	cyclohexyl	MP = 180-183 (dimaleate)
195	2-pyrimidinyl	O	C_6H_5	cyclohexyl	SIMS-NBA-G/TG-DMSO: 429 (M+1), 308, 261
196	propadienyl	O	CH_3	cyclohexyl	MP = 149-152 (dimaleate)
197	4$(CH_3O)C_6H_4$	SO Isomer A	CN Isomer B	cyclohexyl	SIMS-NBA-G/TG-DMSO: 438 (M+1), 411, 395, 331, 254, 246, 214
198	4$(CH_3O)C_6H_4$	SO Isomer A	CH_3	cyclohexyl	SIMS-NBA-G/TG-DMSO: 427 (M+1), 343
200	4$(CH_3O)C_6H_4$	SO iso B	CN iso A	cyclohexyl	SIMS-NBA-G/TG-DMSO: 438 (M+1), 411, 395, 331, 254, 246, 214
201	C_6H_5	O	H	cyclohexyl	CI(CH_4): 351 (M+1)
202	C_6H_5	O	CN	cyclohexyl	SIMS-NBA-G/TG-DMSO: 375 (M+1)
203	6-(MeNH)-3-pyridazinyl	SO_2	CH_3	cyclohexyl	MP = 177-179
204	6-(MeNH)-3-pyridazinyl	SO	CH_3	cyclohexyl	MP = 113-135
205	2-propynyl	S	CH_3	cyclohexyl	170-173 (dimaleate)

207	4-(CH_3O)C_6H_4	S	H	cyclohexyl	CI(Isobutane):(M+1) 397,
208	2-propynyl	NMe	CH_3	cyclohexyl	MP = 73-76
209	2-propynyl	O	CN	cyclohexyl	MP = 128-130 (maleate)
210	6-(MeO)-3-pyridazinyl	SO_2	CH_3	cyclohexyl	MP = 165-167 (dimaleate)
211	4(CH_3O)C_6H_4	SO iso A	CN iso A)	cyclohexyl	SIMS-NBA-G/TG-DMSO: 438 (M+1), 411, 395, 331, 254, 246, 214
212	2-pyrimidinyl	O	cyclohexyl	cyclohexyl	CI(Isobutane): 435 (M+1), 351
213	2-pyrimidinyl	O	CN	cyclohexyl	FAB-NBA-G/TG-DMSO: 378 (M+1), 351
214	4(CH_3O)C_6H_4	SO_2	CO_2CH_3	cyclohexyl	FAB-NBA-G/TG-DMSO:(m+1)487, 455, 429, 391, 232
215	C_6H_5	O	CN	cyclohexyl	CI(CH_4): 376 (M+1), 349
216	4-HO-C_6H_4	SO	CN	cyclohexyl	SIMS-G/TG-DMSO-30%TFA: (M+1) 424, 408, 397, 381
217	4-(CH_3O)C_6H_4	SO_2	cyclohexyl	cyclohexyl	EI: 510, 427
218	4-(CH_3O)C_6H_4	SO	cyclohexyl	cyclohexyl	EI: 494, 411
219	4-(CH_3O)C_6H_4	S	cyclohexyl	cyclohexyl	EI: 478, 395, 328, 245, 229
220	4-(CH_3O)C_6H_4	SO_2	$CONH_2$	cyclohexyl	SIMS-NBA-G/TG-DMSO (M+1) 472, 456, 427, 345, 232
221	4-(CH_3O)C_6H_4	SO	C(NH_2)=NOH	cyclohexyl	FAB-NBA-G/TG-DMSO: (m+1)471, 411, 391, 293, 257, 232,
222	4-(CH_3O)C_6H_4	SO	$CONH_2$	cyclohexyl	FAB-NBA-G/TG-DMSO: 456 (M+1), 411, 349, 272
223	1-propynyl	S	CN	cyclohexyl	MP = 173-175 (maleate)
224	4-(CH_3O)C_6H_4	SO	CO_2CH_3	cyclohexyl	FAB-NBA-G/TG-DMSO: 471 (M+1), 455, 411, 364, 287, 273
225	cyclopropylmethyl	O	CH_3	cyclohexyl	MP = 197-198 (dimaleate)
226	2-propynyl	S	CN	cyclohexyl	123-125 (maleate)
227 (-)	2-pyrimidinyl	O	cyclohexyl	cyclohexyl	CI (CH_4): 435 (M+1), 267
228 (+)	2-pyrimidinyl	O	cyclohexyl	cyclohexyl	CI(CH_4): 435 (M+1), 267

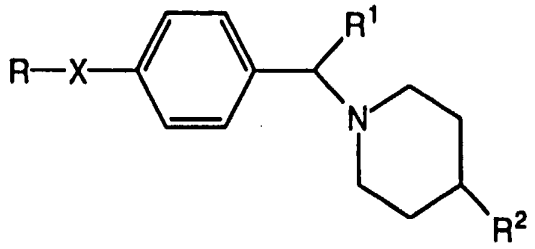
229	1-propynyl	S	cyclohexyl	cyclohexyl	MP = 159-162 (dimaleate)
230	2-butynyl	O	CN	cyclohexyl	MP = 137-140 (maleate)
231	2-pyrimidinyl	O	1-Me-4-piperidynyl	cyclohexyl	EI: 449, 351, 282, 185.
232	2-pyrimidinyl	O	i-Pr	cyclohexyl	SIMS-NBA-G/TG-DMSO: 395 (M+1), 227
233	4(CH_3O)C_6H_4	S	CO_2CH_3	cyclohexyl	SIMS-NBA-G/TG-DMSO: 455 (M+1), 395, 287, 246
234	4(CH_3O)C_6H_4	SO	5-tetrazolyl	cyclohexyl	SIMS-NBA-G/TG-DMSO: (M+1), 481, 465, 456, 411, 395
235	2-pyrimidinyl	O	cyclopentyl	cyclohexyl	M.P. = 165-8 (HCl)
236	4(CH_3O)C_6H_4	SO	2-Me-5-tetrazolyl	cyclohexyl	FAB-NBA-G/TG-DMSO: 495 (M+1), 471, 438, 411, 283, 273, 246, 232
237	4(CH_3O)C_6H_4	S	allyl	cyclohexyl	FAB-NBA-G/TG-DMSO: 437 (M+1), 395, 313, 264, 246, 242
238	2-propynyl	O	CN	cyclohexyl	M.P. = 115-117
239	2-propynyl	O	CH_3	cyclohexyl	M.P. = 178-180 (Dimaleate)
240	4(CH_3O)C_6H_4	SO	3-TMS-4-(1,2,3)-tri-azolyl	cyclohexyl	FAB-NBA-G/TG-DMSO: 552 (M+1), 536, 368, 356, 214
241	2-pyrimidinyl	O	allyl	cyclohexyl	M.P. = 225-7 (HCL)
199	4-(CH_3)-C_6H_4	SO	CON(Me)2	cyclohexyl	FAB-NBA-G/TG-DMSO: 468 (M+1), 431, 395, 304, 300

Compounds having the formula



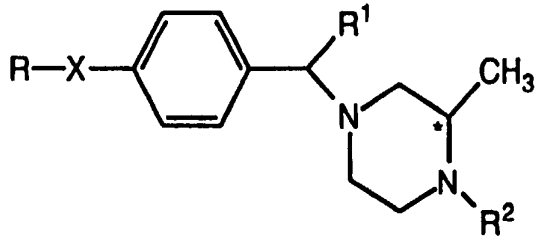
#	R	X	R^1	R^2	Mass Spectrum or MP
242	C_6H_5	SO_2	CH_3	CH_3	EI: 343(M), 125
243	2-pyrimidinyl	O	CN	chex	SIMS-NBA-G/TG-DMSO: 377 (M + 1)
141	C_6H_5	O	H	chex	FAB-NBA-G/TG-DMSO: 350 (M+1)
149	3-Cl-C_6H_5	SO_2	$=CH_2$	CH_3	FAB-NBA-G/TG-DMSO: 376 (M+1)

Compounds having the formula



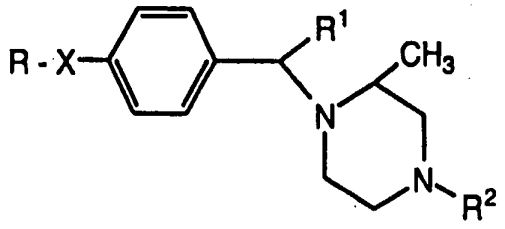
#	R	X	R^1	R^2	Mass Spectrum or MP
244	C_6H_5	SO_2	i-Pr	$N(CH_3)_2$	FAB-NBA-G/TG-DMSO: (M+1) 401, 356, 312, 273
245	C_6H_5	SO_2	C_6H_5	1-piperidyl	$Cl(CH_4)$: (M+1) 475, 307
246	4-CH_3-C_6H_4	SO_2	i-Pr	1-piperidyl	
247	2-pyrimidinyl	O	CH_3	CH_3	$Cl(CH_4)$: 298 (M+1), 282, 199, 126. Cl(City)
248	4-CH_3-C_6H_4	SO_2	CH_3	CH_3	EI: 358 (M+1), 342
249	4-CH_3-C_6H_4	SO_2	CH_3	CO_2Et	SIMS-NBA-G/TG-DMSO: 416 (M+1)
250	4-CH_3-C_6H_4	SO_2	CH_3	benzyl	SIMS-NBA-G/TG-DMSO: 434 (M+1)
251	2-pyrimidinyl	O	CH_3	1-piperidyl	$Cl(CH_4)$: 367 (M+1) 281, 199, 167
252	2-pyrimidinyl	O	CH_3	chex	SIMS-NBA-G/TG-DMSO: 366 (M+1), 350
253	C_6H_5	SO_2	H	$(CH_2)_3N(Et)COC(Me)_2$ n-C_3H_7	SIMS-NBA-G/TG-DMSO: 513 (M+1)
254	C_6H_5	SO_2	CH_3	CH_3	Cl (CH_4): 344 (M+1)
255	C_6H_5	SO_2	CH_3	chex	$Cl(CH_4)$: 412 (M+1)
256	C_6H_5	O	CH_3	CH_3	$Cl(CH_4)$: 296 (M+1)
82	4-CH_3-C_6H_6	SO_2	CH_3	chex	$Cl(CH_4)$: 426 (M+1) 342, 270, 166

Compounds having the formula



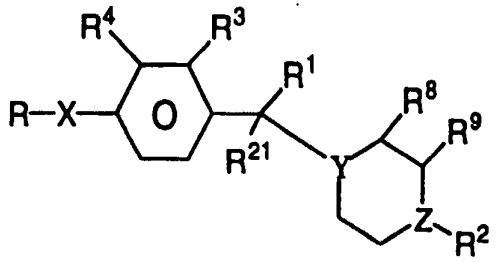
	#	R	X	R^1	R^2	*	Mass Spectrum or MP
	257	C_6H_5	SO_2	H	chex		SIMS-G/TG-DMSO: 413 (M+1)
	258	C_6H_5	SO_2	H	chex	Isomer A	SIMS-NBA-G/TG-DMSO: 413 (M+1)
	259	C_6H_5	SO_2	H	chex	Isomer B	CI(CH_4): 413 (M+1)
	260	3-Cl-C_6H_4	SO_2	CH_3	chex	Isomer B	SIMS-NBA-G/TG-DMSO: 463, 461 (M+1)
	261	2-pyrimidinyl	O	CH_3	chex	Isomer A	CI (CH_4): 381 (M+1), 199.
	262	2-pyrimidinyl	O	CH_3	chex	Isomer B	SIMS-NBA-G/TG-DMSO: 381 (M+1)
	263 iso A	4(CH_3O)C_6H_4	SO	CN	chex	Isomer A	SIMS-NBA-G/TG-DMSO: 452 (M+1)
	206 isoB	4-CH_3O-C_6H_4 SO	SO	CN	chex	Isomer B	CI(Isobutane): 452 (M + 1), 425

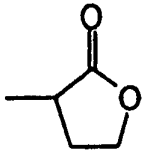
Compounds having the formula

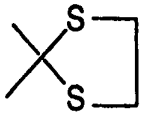
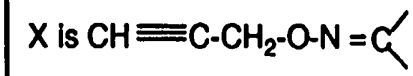


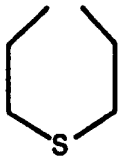
#	R	X	R^1	R^2	*	Mass Spectrum or MP=
265	C_6H_5	SO_2	H	chex		EI: 412, 369, 181, 126.
266	C_6H_5	SO_2	H	chex	Isomer A	SIMS-NBA-G/TG-DMSO: 413 (M+1)
267	C_6H_5	SO_2	H	chex	Isomer B	CI(CH_4): 413 (M+1)
268	C_6H_5	SO_2	CH_3	chex		CI(CH_4): 427 (M + 1)
269	2-pyrimidinyl	O	CH_3	chex		SIMS-NBA-G/TG-DMSO: 381 (M+1), 199
270	2-pyrimidinyl	O	1-Me-4-piperidinyl	chex		CI(CH_4): 464 (M+1), 462, 282
271	2-pyrimidinyl	O	i-Pr	chex		SIMS-NBA-G/TG-DMSO: 409 (M+1), 227
272	2-pyrimidinyl	O	H	chex		CI(CH_4): 367 (M+1)
273	2-pyrimidinyl	O	n-hexyl	chex		SIMS-NBA-G/TG-DMSO: 451 (M+1), 269
274 Iso.A	2-pyrimidinyl	O	chex	chex		CI(CH_4): 449 (M+1), 365, 267
275 Iso.B	2-pyrimidinyl	O	chex	chex		CI(CH_4): 449 (M+1), 365, 267
157	C_6H_5	SO_2	H	2-cyclohex-enyl		SIMS-NBA-G/TG-DMSO: 411 (M+1)

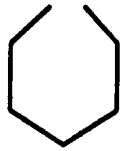
Compounds having the formula



#	Mass Spectrum or MP
280	R is 4-CH_3-C_6H_4: X is SO_2: R^1 is CH_3; R^2 is  ; R^3, R^4, R^8, R^9, and R^{21} are H; Y and Z are N mass spec CI(CH_4): 429 (M+1)
281	R is 4-CH_3-C_6H_4; X is SO_2; R^1 is CH_3; R^2 is chex; R^3 is OCH_3; R^4, R^8, R^9, and R^{21} are H; and Y and Z are N mass spec CI(CH_4): 457 (M+1)
282	R is 4-CH_3-C_6H_4; X is SO_2; R^1 is CH_3; R^2 is chex; R^3 is H; R^4 is F; R^8, R^9, and R^{21} are H; Y and Z are N mass spec CI(CH_4):(M+1) 445, 289, 277, 195, 167
283	R is C_6H_5; X is SO_2; R^1 is CH_3; R^2 is chex; R^3 is Cl; R^4, R^8, R^9, and R^{21} are H; Y and Z are N; mass spec CI(CH_4): 449, 447, (M+1)

284	R is 4-CH_3-C_6H_4; X is SO_2; R^1 is CH_3; R^2, R^3 and R^4 are H; R^9 is CH_2OH; R^4 and R^{21} are H; Y is N; Z is CH_2; mass spectrum CI(CH_4); 374 (M+1), 261.
285	R is 4-(CH_3O)C_6H_4; X is  ; R^1 is CH_3; R^2 is chex; R^3, R^4, R^8, R^9, and R^{21} are H, Y and Z are N mass spectrum EI: (M+1) 482, 467, 439, 343, 255, 211, 167
286	R is CH_3;  R^1 is CH_3; R^2 is chex; R^3, R^4, R^8, R^9 and R^{21} are H; Y and Z are N MP = 173-175 dimaleate
287	R is C_6H_5; X is SO_2; R^1 is H, R^2 is chex; R^3 is Cl; R^4 and R^5 are H; R^9 is (R)-CH_3, R^{21} is H; Y and Z are N; mass spec CI(CH_4): 447 (M+1)
288	R is 4-(CH_3O)-C_6H_4; X is SO; R^1 is CN; R^2 is chex; R^3, R^4, R^8, and R^9 are H; R^{21} is $CH_2CO_2CH_3$; Y and Z are N; mass spec SIMS-NBA-G/TG-DMSO) 510.2 (M+1) 483.2, 307.1, 273.1, 246.1, 214
289	R is 4-(CH_3O)-C_6H_4; X is SO; R^1 is CN; R^2 is chex; R^3, R^4, R^8, and R^9 are H; R^{21} is CH_3; Y and Z are N mass spec SIMS-NBA-G/TG-DMSO: 452.2 (M+1), 425.2, 293.1, 268.1, 257.1
290	R is 4-(CH_3O)-C_6H_4; X is SO; R^1 is CN; R^2 is chex; R^3, R^4, R^8, and R^9 are H; R^{21} is CO_2Me; Y and Z are N mass spec FAB-NBA-G/TG-DMSO: 496 (M+1), 480, 469, 454, 389, 312
291	R is 2-pyrimidinyl; X is O; R^1 is CH_3; R^2 is chex; R^3 and R^4 are H; R^8 is (S)-CH_3; R^9 and R^{21} are H; Y and Z are N; mass spec FAB-NBA-G/TG-DMSO: 381 (M + 1), 199.

292	R is 2-pyrimidinyl; X is O; R^1 is H; R^2 is chex; R^3 and R^4 are H; R^8 is (S)-CH_3; R^9 and R^{21} are H; Y and Z are N; mass spec FAB-NBA-G/TG-DMSO: 267 (M + 1)
293	R is 2-pyrimidinyl; X is O; R^1 is H; R^2 is chex; R^3 and R^4 are H; R^8 is (R)-CH_3; R^9 and R^{21} are H; Y and Z are N; mass spec FAB-NBA-G/TG-DMSO: 367(M + 1)
294	R is 2-pyrimidinyl; X is O; R^1 is CH_3; R^2 is chex; R^3 and R^4 are H; R^8 is (R)-CH_3; R^9 and R^{21} are H; Y and Z are N; M.P. =170-173 (HCL)
295	R is 4-(CH_3O)-C_6H_4; X is SO; R^1 is CN; R^2 is chex; R^3, R^4, R^8 and R^9 are H; R^{21} is CN; Y and Z are N; mass spec FAB-NBA-G/TG-DMSO: 463 (M+1), 436, 356, 307, 273
296	R is 4(CH_3O)-C_6H_4; X is SO; R^1 is CH_3; R^2 is chex; R^3, R^4, R^8, and R^9 are H; R^{21} is CO_2Me; Y and Z are N; mass spec FAB-NBA-G/TG-DMSO: 485 (M+1), 471, 425, 381, 365, 338, 320
297	R is 2-propynyl; X is O; R^1 is CH_3; R^2 is chex; R^4 is Cl; R^3, R^8, R^9, and R^{21} are H; Y and Z are N M.P. = 172-174 (dimaleate)
298	R is 4-(CH_3O)-C_6H_4; X is SO; R^1 is CN; R^2 is chex; R^3, R^4, R^8 and R^9 are H; R^{21} is allyl; Y and Z are N; mass spec FAB-NBA-G/TG-DMSO: 478 (M+1), 451, 354, 294, 246
299	R is 2-propynyl; X is O; R^1 is CN; R^2 is chex; R^4 is Cl; R^3, R^8, R^9 are R^{21} are H; Y and Z are N M.P. = 132-134 (maleate)
300	R is 4(CH_3O)-C_6H_4; X is SO; R^1 and R^{21} togehter form =CH_2; R^2 is cyclohexxyl, y is CH, Z is N, R^3, R^4, R^8 and R^9 are H - sulfoxide isomer A
301	R is 4(CH_3O)-C_6H_4; X is SO; R^1 and R^{21} togehter form =CH_2; R^2 is cyclohexxyl, y is CH, Z i N, R^3, R^4, R^8 and R^9 are H - sulfoxide isomer B; mp = 141-142
302	R is 4(CH_3O)- C_6H_4; X is S; R^1 and R^{21} together form =CH_2; R^2 is cyclohexyl, Y is CH, Z is N, R^3, R^4, R^8 and R^9 are H; mp = 227-230 (HCl)
303	 R^1 is C_6H_5; X is O; R^1 and R^{21} together form ; Y and Z are N; R^2 is cyclohexyl; R^3, R^4, R^8 and R^9 are H; mp = 137-139

304	R is 4(CH_3O)-C_6H_4; X is SO; R^1 and R^{21} togehter form =CH_2; R^2 is cyclohexyl, y is CH, Z is N, R^3, R^4, R^8 and R^9 are H - racemic mixture; mp = 122
305	R is 4(H_3CO)-C_6H_4; X is SO; R^1 and R^{21} together form =O; R^2 is cyclohexyl; Y is CH; Z is N; R^3, R^4, R^8 and R^9 are H.
306	R is C_6H_5, X is O, R^1 and R^{21} together form  , and Y and Z are N, R^3, R^4, R^8 and R^9 are H; mp = 144-146 (dimaleate)

In like manner compounds 600 to 804 from the previous table were produced with the following physical data:

Compound Number	Melting Point or Mass Spectral Data
600	FAB (NBA-G/TG-DMSO): 435 (M+1), 391, 338, 324
601	mp=164-167
602	MS CALC'D 461.2030 FOUND 461.2040
603	MS CALC'D 425 FOUND 425
604	FAB (NBA-G/TG-DMSO): 471 (M+1), 455, 411, 364, 287
605	mp=64-68
606	mp=194-195
607	Mass Spec CI (ISOB): 408 (M+1), 381, 365, 231, 169
608	MS CALC'D 453 FOUND 453
609	Mass Spec SIMS (NBA-G/TG-DMSO): 452 (M+1), 425, 409, 293, 232
610	Mass Spec FAB(NBA-G/TG-DMSO):544(M+1),543,516,232
611	MS CALC'D 467 FOUND 467
612	mp=142-145
613	Mass Spec CI : 452 (M+1)
614	MS CALC'D 437 FOUND 437
615	Mass Spec SIMS (NBA-G/TG-DMSO): 452 (M+1), 425, 409, 293, 232
616	MS CALC'D 389 FOUND 390
617	Mass Spec FAB(NBA-G/TG-DMSO):560(M+1),559,532,433,363
618	mp=143-145
619	
620	mp=123-124
621	Mass Spec FAB (NBA-G/TG-DMSO): 495 (M+1), 411, 299, 283
622	mp=205
623	mp=212
624	Mass Spec FAB(NBA-G/TG-DMSO):544(M+1),543,516
625	mp=132-134
626	Mass Spec FAB(NBA-G/TG-DMSO):514(M+1),513,486,240
627	Mass Spec FAB(SIMS9CAL):530(M+1),425,398
628	mp=141-145
629	mp=151-154
630	Mass Spec FAB(NBA-G/TG-DMSO):560(M+1),559,532
631	Mass Spec FAB(SIMS4CAL):515(M+1),514,487,307,289,238
632	mp=121-124 MS CALC'D 410 FOUND 410
633	MS CALC'D 438.2200 FOUND 438.2215
634	Mass Spec CI : 436 (M+1), 409
635	mp=190 (dec)
636	MS CALC'D 381 FOUND 382
637	mp=225
638	MS CALC'D 441 FOUND 442
639	mp=253-255
640	Mass Spec FAB(NBA-G/TG-DMSO):409(M+1),381
641	MS CALC'D 454 FOUND 455
642	mp=245
643	mp=209
644	MS CALC'D 419.2698 FOUND 419.2706
645	mp=248-250
646	mp=132-133 MS CALC'D 439 FOUND 439

647	MS CALC'D 454 FOUND 455
648	mp=210-211
649	mp=250
650	mp=200-203
651	MS CALC'D 380.2048 FOUND 380.2047
652	mp=129-131 MS CALC'D 439 FOUND 439
653	mp=188-189
654	MS CALC'D 394.2205 FOUND 394.2199
655	MS CALC'D 451.2419 FOUND 451.2404
656	mp=227-230
657	MS CALC'D 452 FOUND 452
658	mp=53-55
659	MS CALC'D 412.2110 FOUND 412.2111
660	MS CALC'D 412.1946 FOUND 412.1950
661	HRMS Calcd 455.2368 Found 455.2370
662	MS CALC'D 430.1852 FOUND 430.1856
663	mp=159-163 MS CALC'D 439 FOUND 440
664	MS CALC'D 471.2318 FOUND 471.2327
665	MS CALC'D 381.2001 FOUND 381.2000
666	MS CALC'D 410.2154 FOUND 410.2158
667	mp=241-242
668	MS CALC'D 470.2367 FOUND 470.2367
669	mp=168-170 MS CALC'D 440 FOUND 441
670	MS CALC'D 414.1903 FOUND 414.1899
671	mp=130.5-131.5
672	Mass Spec CI (CH4): 481 (M+1), 465, 445, 357, 297, 249, 167
673	MS CALC'D 379.2208 FOUND 379.2210
674	MS:calcd for C28H35NSO4: 481 found 481.7.
675	MS CALC'D 395.2157 FOUND 395.2161
676	MS:calcd for C29H37NSO4: 495; found 494 (M+1).
677	mp=150-151
678	Mass Spec CI (CH4): 497 (M+1), 477, 325, 167
679	MS CALC'D 387 FOUND 388
680	MS CALC'D 413.1899 FOUND 413.1892
681	MS CALC'D 411.2106 FOUND 411.2100
682	MS:calcd for C32H37NSO2: 499; found 500 (M+1).
683	MS CALC'D 381.2001 FOUND 381.1996
684	MS CALC'D 478.2028 FOUND 478.2014
685	MS:calcd for C29H37NSO3: 479; found 480.4 (M+1).
686	MS CALC'D 397.1950 FOUND 397.1954
687	MS CALC'D 462.2078 FOUND 462.2078
688	MS:calcd for C32H37NSO3: 515; found 516 (M+1).
689	MS CALC'D 413.1899 FOUND 483.1892
690	MS CALC'D 379.2208 FOUND 379.2203
691	MS CALC'D 437.2263 FOUND 437.2264
692	MS CALC'D 395.2157 FOUND 395.2169
693	MS CALC'D 442.2052 FOUND 442.2057
694	MS CALC'D 442.2052 FOUND 442.2057
695	MS CALC'D 456.2572 FOUND 456.2580

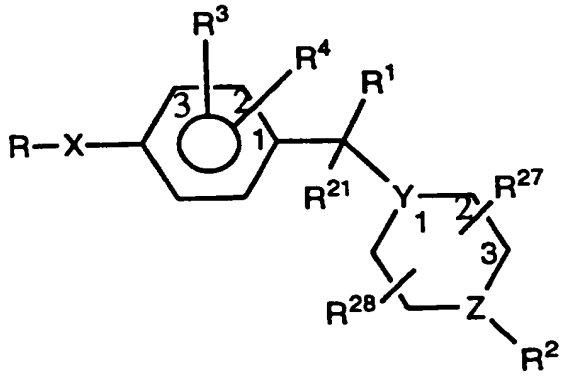
696	MS CALC'D 391 FOUND 391
697	MS CALC'D 397.1950 FOUND 397.1954
698	MS CALC'D 516.2572 FOUND 516.2572
699	MS CALC'D 410.2154 FOUND 410.2154
700	mp=215-218
701	MS CALC'D 456 FOUND 457
702	MS CALC'D 437.2263 FOUND 437.2269
703	MS CALC'D 411.2106 FOUND 411.2104
704	MS CALC'D 426.2103 FOUND 426.2117
705	MS CALC'D 440.2623 FOUND 440.2632
706	mp=215-218
707	m.p. = 165.0 - 170.0°C (•2HCl)
708	m.p. = 155.0 - 160.0°C (•2HCl)
709	MS CALC'D 470.2001 FOUND 470.2007
710	mp=248-250
711	MS:calcd for C30H40N2SO5: 540; found 541 (M+1).
712	MS CALC'D 510.2790 FOUND 510.2787
713	MS CALC'D 466 FOUND 467
714	m.p. = 141.0 - 142.0°C (free base)
715	Mass Spec FAB: 485 (M+1), 441, 253, 209
716	MS CALC'D 428.1896 FOUND 428.1904
717	MS:calcd for C25H32N2SO3: 440; found 441.2 (M+1).
718	MS CALC'D 420 FOUND 421
719	MS CALC'D 514 FOUND 515
720	m.p. = 90.0 - 95.0°C (free base)
721	Mass Spec FAB: 485 (M+1), 391, 273, 232
722	MS CALC'D 496.1769 FOUND 496.1765
723	MS CALC'D 497.2474 FOUND 497.2460
724	MS CALC'D 466 FOUND 467
725	MS CALC'D 498 FOUND 499
726	mp=200-210 (dec) , Mass Spec MH+ =433
727	mp=210 (dec)
728	mp=22o deg (dec)
729	MS CALC'D 427.2419 FOUND 427.2427
730	
731	mp=180 (dec)
732	mp=200 (dec), Mass Spec MH+ =433
733	mp=180 deg (dec)
734	mp=215 deg (dec)
735	MS CALC'D 443.2368 FOUND 443.2367
736	mp=210 deg (dec)
737	mp=200 deg (dec)
738	mp=205 deg (dec)
739	mp=210 deg (dec)
740	
741	mp=205 deg (dec)
742	mp=185 deg (dec)
743	mp=120-123
744	mp=125-128

745	mp=130-133
746	Mass Spec FAB(NBA-G/TG-DMSO):480(M+1),479,452,311
747	mp=208-211
748	MS CALC'D 427 FOUND 428
749	mp=131-134
750	161-163
751	FAB MS 648(MH+)
752	Mass Spec FAB(NBA-G/TG-DMSO):511(M+1),484
753	FAB: 495 (M+1), 479, 411, 311
754	MS CALC'D 439 FOUND 440
755	MS CALC'D 440.2259 FOUND 440.2255
756	MS CALC'D 470 FOUND 470
757	mp=131-132.5
758	MS:calcd for C26H35NSO2: 425; found 426.3 (M+1).
759	MS CALC'D 455 FOUND 456
760	MS:calcd for C28H36N2SO5: 512; found 513.2 (M+1).
761	MS CALC'D 456 FOUND 456
762	mp=165-166 MS CALC'D 437 FOUND 438
763	MS:calcd for C28H36N2SO4: 496; found 497.3 (M+1).
764	MS:calcd for C26H33NSO2: 423; found 424.3 (M+1).
765	MS:calcd for C28H36N2SO3: 480; found 481.6 (M+1).
766	MS:calcd for C26H35NSO4: 457; found 458 (M+1).
767	MS:calcd for C26H35NSO3: 441; found 442(M+1).
768	mp=149-150
769	MS:calcd for C28H37NSO4: 483; found 484 (M+1).
770	MS CALC'D 476.2071 FOUND 476.2066
771	MS:calcd for C28H38N2SO5: 514; found 515.3 (M+1).
772	mp=142-143
773	mp=143-144
774	MS:calcd for C28H37NSO5: 499; found 500 (M+1).
775	MS CALC'D 460 FOUND 460
776	MS:calcd for C29H37NSO5: 511; found 512 (M+1).
777	MS:calcd for C28H41N3S2O5: 563; found 564.1(M+1).
779	m.p. = 150.0 - 152.0°C (•2HCl)
780	m.p. = 187.0 - 189.0°C (•2HCl)
781	MS:calcd for C25H31NSO4: 441; found 442 (M+1).
782	MS:calcd for C25H31NSO2: 409; found 410 (M+1).
783	MS:calcd for C28H39N3SO5: 529; found 530.7 (M+1).
784	m.p. = 155.0 - 157.0°C (•2HCl)
785	m.p. = 135.0 - 137.0°C (•2HCl)
786	MS calc'd 511.2994 found: 511.3000
787	MS:calcd for C25H31NSO3: 425; found 426 (M+1).
788	MS:calcd for C28H39N3SO5: 529; found 530.3 (M+1).
789	MS:calcd for C28H39N3SO3: 497; found 498.4 (M+1).
790	MS:calcd for C28H39N3SO3: 497; found 498.3 (M+1).
791	MS:calcd for C29H41N3SO4: 527; found 528.1 (M+1).
792	mp=205-210
793	Mass Spec CI : 375 (M+1)
794	mp=150-152

795	mp=224-227
796	MS:calcd for C30H43N3SO3: 525; found 526 (M+1).
797	MS:calcd for C28H40N4SO4: 528; found 529.1 (M+1).
798	Mass Spec CI : 441 (M+1)
799	mp=138-140
800	mp=143-146
801	mp=259
802	mp=120-122
803	mp=215-225 (dec) Mass Spec MH+ =473
804	mp=195-205 (dec) Mass Spec MH+ =473
805	mp=228-230 (dec)

What is Claimed:

1. A compound having the structural formula I,

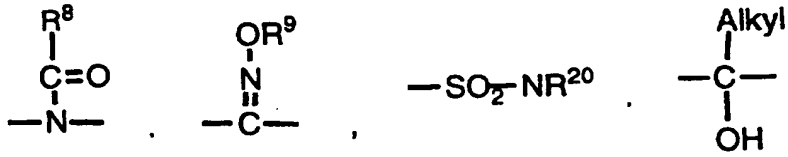


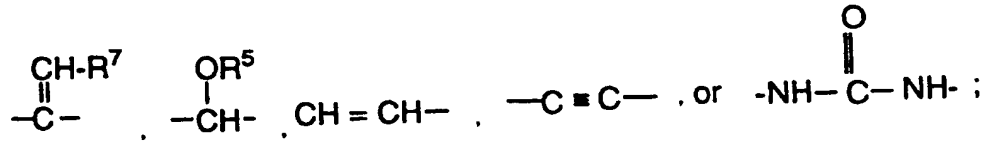
I

including all isomers and pharmaceutically acceptable salts, esters, and solvates thereof,

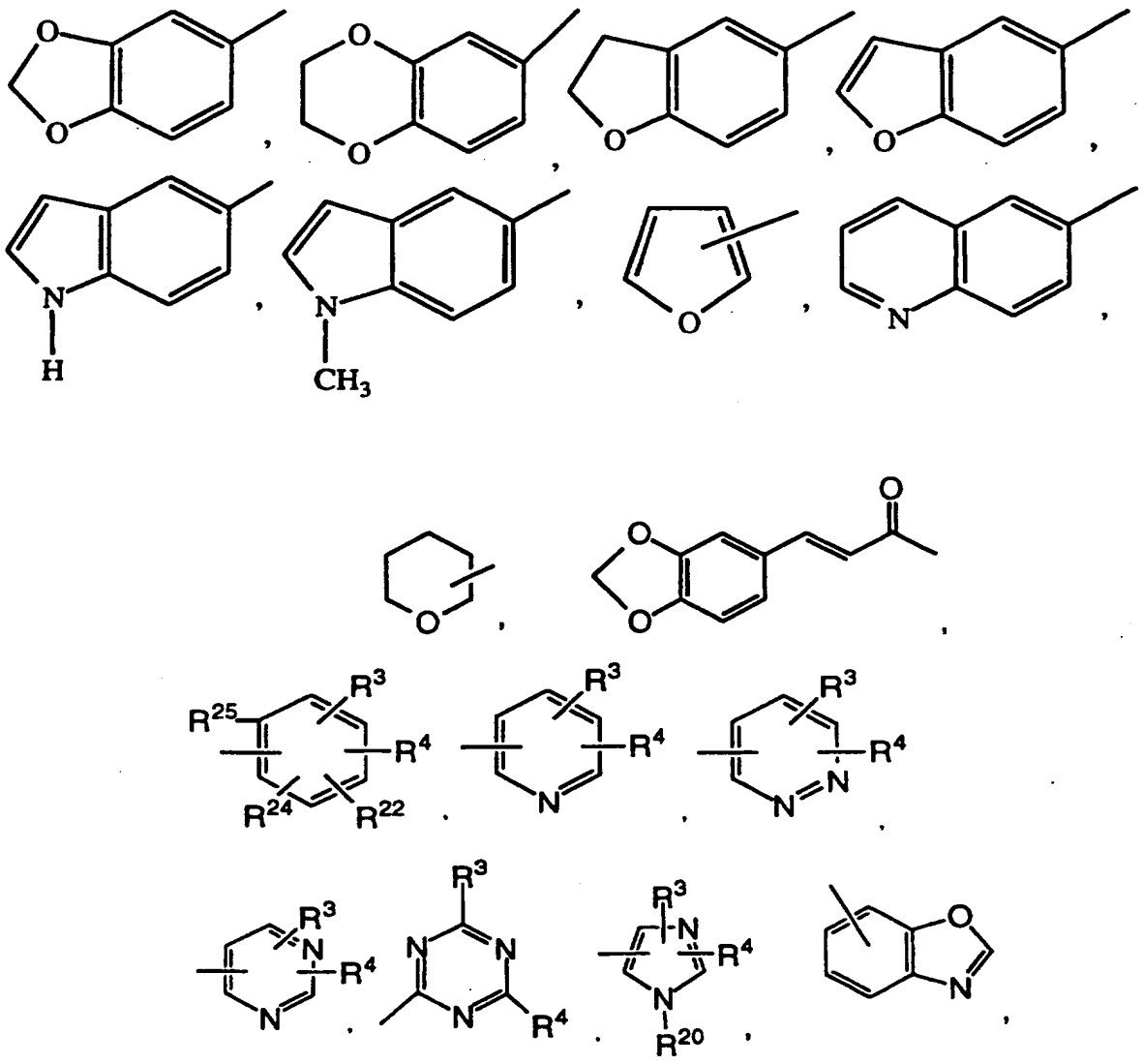
wherein one of Y and Z is N and the other is N, CH, or C-alkyl;

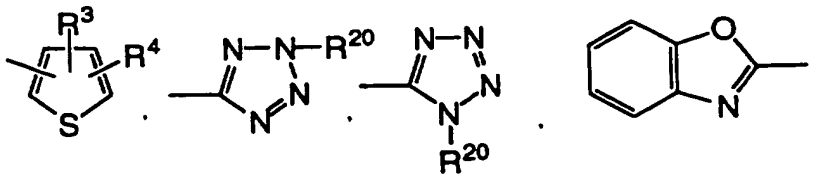
X is -O-, -S-, -SO-, $-SO_2-$, $-NR^6-$, -CO-, $-CH_2-$, -CS-, $-C(OR^5)_2-$, $-C(SR^5)_2-$, $-CONR^{20}-$, $-C(alkyl)_2-$, -C(H)(alkyl)-, $-NR^{20}-SO_2-$, $-NR^{20}CO-$,

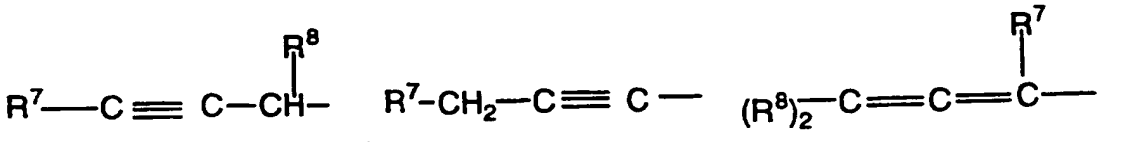


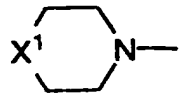


R is

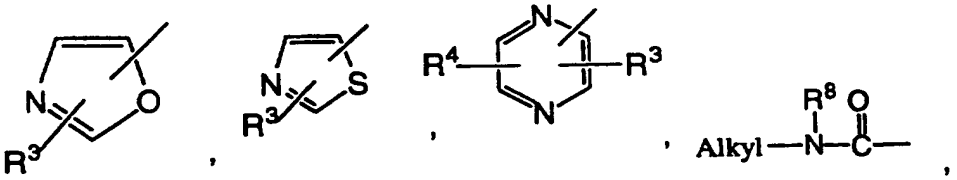


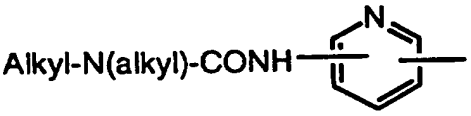


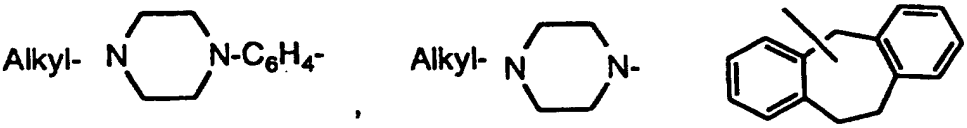




(wherein X^1 is $-CH_2-$, -O-, or $-NR^7-$),



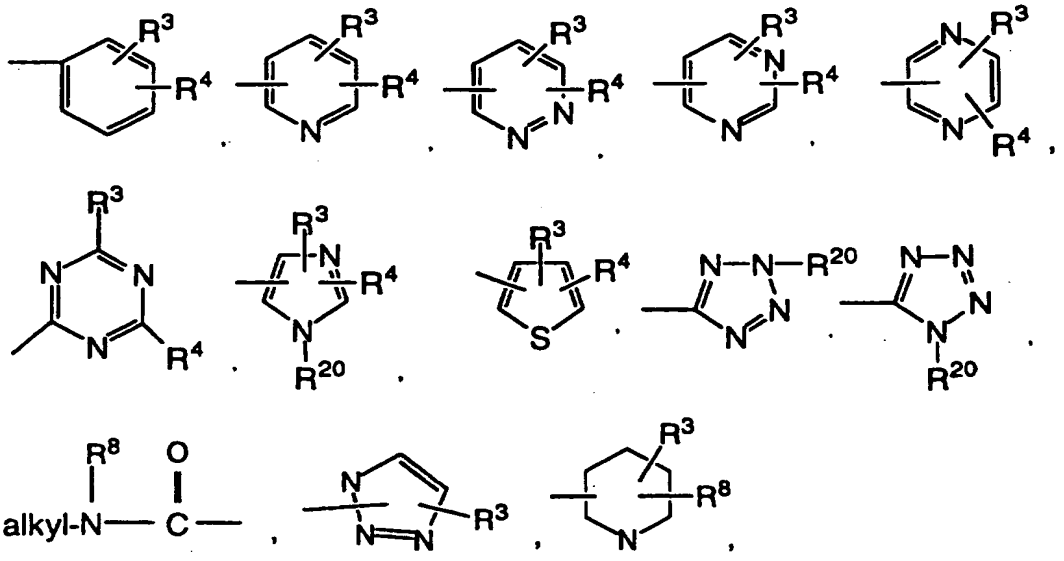




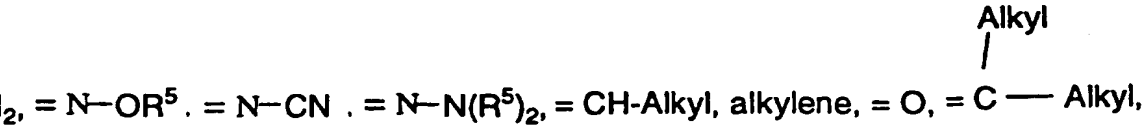
hydrogen, acyl, alkyl, alkenyl, cycloalkyl, cycloalkyl substituted with up to two alkyl groups, cycloalkenyl, bicycloalkyl, arylalkenyl, benzyl, benzyl substituted with up to three independently selected R^3 groups, cycloalkylalkyl, polyhaloacyl, benzyloxyalkyl, hydroxyC_2-C_{20}alkyl, alkenylcarbonyl, alkylarylsulfonyl, alkoxycarbonylaminoacyl, alkylsulfonyl, or arylsulfonyl, additionally, when X is $-CH_2-$, R may also be -OH; in further addition, when X is not N, R may also be hydroxymethyl, in further addition, R and X may combine to

form the group Prot-(NOAA)$_r$-NH- wherein r is an integer of 1 to 4, Prot is a nitrogen protecting group and when r is 1, NOAA is a naturally occuring amino acid or an enantiomer thereof, or when r is 2 to 4, each NOAA is a peptide of an independently selected naturally occuring amino acid or an enantiomer thereof;

R^1 and R^{21} are independently selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkyl, alkynyl, cyano, aminoalkyl, alkoxycarbonyl, aminocarbonyl, hydroxyguanidino, alkoxycarbonylalkyl, phenyl alkyl, alkylcarbonlyoxyalkyl,

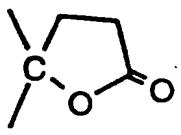


H, —OH, (provided R^1 and R^{21} are both not —OH and Y is not N), formyl, —CO alkyl, -COacyl, —COaryl, and hydroxyalkyl; additionally R^1 and R^{21} together may form the group



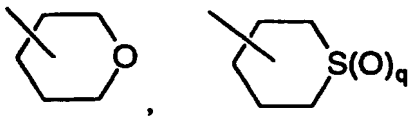
$=CH_2$, $=N-OR^5$, $=N-CN$, $=N-N(R^5)_2$, =CH-Alkyl, alkylene, =O, $=C(\text{Alkyl})-\text{Alkyl}$,

$=C(halo)_2$, in further addition, R^1 and R^{21} together with the carbon atom to which they are attached may form the group

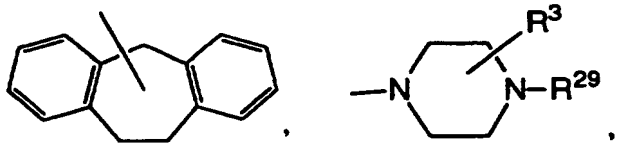


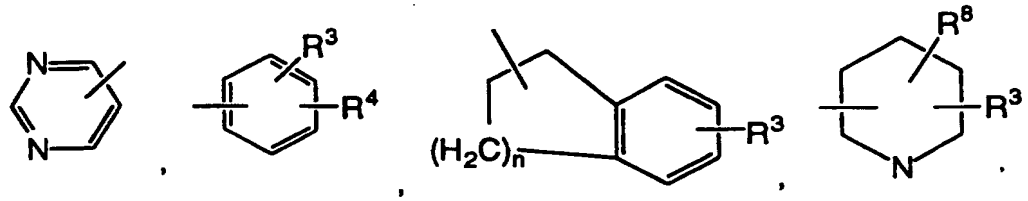
or R^1 and R^{21} together with the carbon atom to which they are attached may form a saturated heterocyclic ring containing 3 to 7 carbon atoms and one group selected from S, O, and NH;

R^2 is H, alkyl, alkenyl, cycloalkyl, cycloalkyl substituted with 1 to 3 independently selected R^3 groups, cycloalkenyl, hydroxyC_2-C_{20}alkyl, alkynyl, alkylamide, cycloalkylalkyl, hydroxyarylalkyl, bicycloalkyl, alkynyl, acylaminoalkyl, arylalkyl, hydroxyalkoxyalkyl, azabicyclo, alkylcarbonyl. alkoxyalkyl, aminocarbonylalkyl, alkoxycarbonylaminoalkyl, alkoxycarbonylamino(alkyl)alkyl; alkylcarbonyloxyalkyl, arylhydroxyalkyl, alkylcarbonylamino(alkyl)alkyl, dialkylamino,

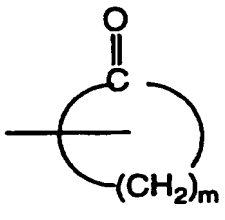


(wherein q is an integer of 0 to 2)

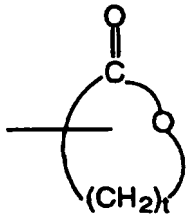




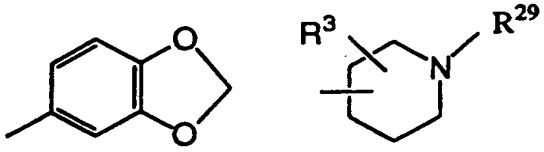
wherein n is 1-3



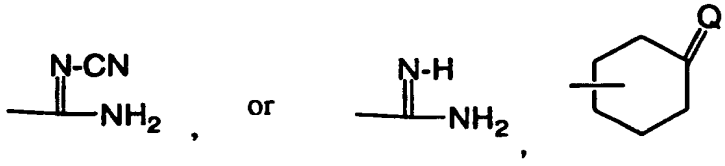
wherein m is an integer of 4 to 7,



wherein t is an integer of 3 to 5,



(wherein R^{29} is H, alkyl, acyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylsulfonyl, arylsulfonyl),



(wherein Q is O, NOH, or NO-alkyl), or when Z is -CH-, R^2 may also be alkoxycarbonyl, hydroxymethyl, $-N(R^8)_2$;

R^3, R^4, R^{22}, R^{24}, and R^{25} are independently selected from the group consisting of H, halo, alkoxy, benzyloxy, benzyloxy substituted by nitro or aminoalkyl, haloalkyl, polyhaloalkyl, nitro, cyano, sulfonyl, hydroxy, amino, alkylamino, formyl, alkylthio, polyhaloalkoxy, acyloxy, trialkylsilyl, alkylsulfonyl, arylsulfonyl, acyl, alkoxycarbonyl alkylsulfinyl; $-OCONH_2$, -OCONH-alkyl, $-OCON(alkyl)_2$, -NHCOO-alkyl, -NHCO-alkyl, phenyl, hydroxyalkyl, or morpholino;

each R^5 and R^6 is independently selected from the group consisting of H and alkyl, provided that when X is $C(OR^5)_2$ or $C(SR^5)_2$, both R^5 groups cannot be H, and in addition, when X is $C(OR^5)_2$ or $C(SR^5)_2$, the two R^5 groups in X may be joined to form $—(CH_2)_p-$ wherein p is an integer of 2 to 4;

R^7 is independently selected from the group consisting of H, alkyl, arylalkyl, cycloalkyl, aryl and aryl substituted with R^3 and R^4 as defined herein;

each R^8 is independently selected from the group consisting of H, hydroxyalkyl, or alkyl or two R^8 groups may be joined to form an alkylene group;

R^9 is H, alkyl, or acyl:

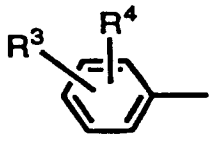
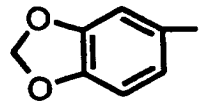
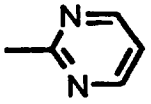
R^{20} is H, phenyl or alkyl; and

R^{27} and R^{28} are independently selected from the group consisting of H, alkyl, hydroxyalkyl, arylalkyl, aminoalkyl, haloalkyl, thioalkyl, alkylthioalkyl, carboxyalkyl, imidazolyalkyl, and indolyalkyl, additionally R^{27} and R^{28} may combine to form an alkylene group..

2. A compound of claim 1 wherein Y and Z are N

3. A compound of claim 1 wherein Y is CH and Z is N

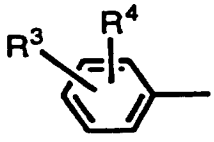
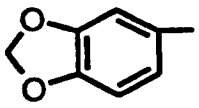
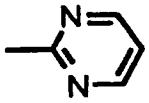
4. A compound of claim 1 wherein R is


, 
, or 

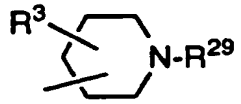
and X is O, SO or SO_2.

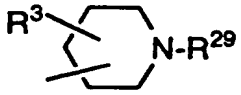
5. A compound of any one of claims 1 or 4 wherein R^3 and R^4 are H and either R^1 is cycloalkyl, alkyl, or CN and R^{21} is H or R^1 and R^{21} together form $=CH_2$ or =O.

6. A compound of any one of claims 1, 4, or 5 wherein R is


, 
, or 
,

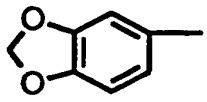
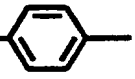
X is O , SO or SO_2, R^3 and R^4 are H and either R^1 is cycloalkyl, alkyl, or CN and R^{21} is H or R^1 and R^{21} togather form $=CH_2$ or =O.

7. A compound of claim 6 wherein Y and Z are N, R^1 is cycloalkyl, alkyl or CN, R^{21} is H and R^2 is cycloalkyl or  .

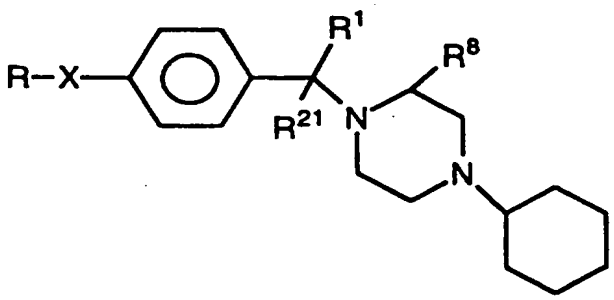
8. A compound of claim 6 wherein Y is CH, Z is N, and R^2 is cycloalkyl or  .

9. A compound of claim 7 wherein at least one of R^{27} and R^{28} is alkyl.

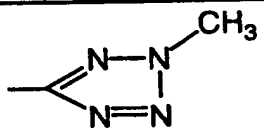
10. A compound of claim 9 wherein one of R^{27} or R^{28} is methyl and the other is hydrogen.

11. A compound of any one of claims 7, 8, 9, or 10 wherein R is  or alkoxy 

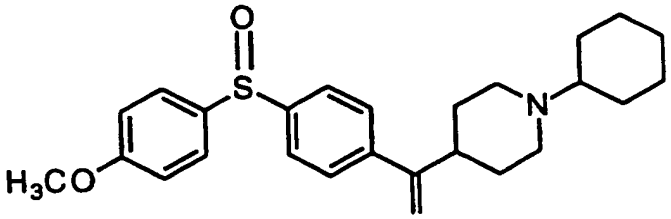
12. A compound as defined in claim 1 selected from the group consisting of compounds represented by the formula



wherein R, X, R^1, R^8, and R^{21} are as defined in the following table

# from table of compounds	R	X	R^1	R^{21}	R^8
169	4(CH_3O)-C_6H_4	SO iso A	CN	H	H
227(-)	2-pyrimidinyl	O	cyclohexyl	H	H
289	4(CH_3O)-C_6H_4	SO	CN	CH_3	H
269	2-pyrimidinyl	O	CH_3	H	CH_3
214	4(CH_3O)-C_6H_4	SO_2	CO_2CH_3	H	H
232	2-pyrimidinyl	O	i-propyl	H	H
123	4(CH_3O)-C_6H_4	SO	CH_3	H	H
236	4(CH_3O)-C_6H_4	SO		H	H
296	4-(CH_3O)-C_6H_4	SO	CH_3	CO_2Me	H

or having the structural formula



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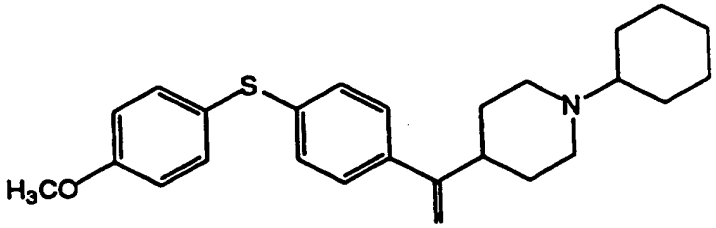
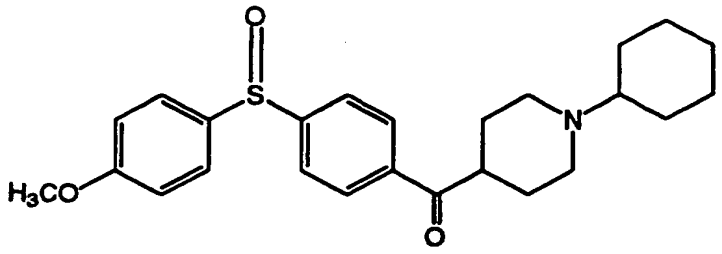


, or



13. A compound of claim 1 selected from the group consisting of compounds numbers 600 to 805 of the table of such compounds appearing in the specification.

14. A pharmaceutical composition which comprises a compound as defined in any one of claims 1 to 13 in combination with a pharmaceutically acceptable carrier.

15. A method for treating a cognitive or neurodegenerative disease comprising administering to a patient suffering from said disease an effective amount of a compound of any of of claims 1 to 13.

16. A method of treating a cognitive or neurodegenerative disease comprising administering to a patient suffering from said disease an effective amount of a combination of a compound of any one of claims 1 to 13 with an acetylcholinesterase inhibitor.

17. A method of treating a cognitive or neurodegenerative disease comprising administering to a patient suffering from said disease an effective amount of a combination of an acetylcholine release enhancing compound with an acetylcholinesterase inhibitor.

18. The method of claim 17 wherein the acetylcholine release enhancing compound is an m2 selective muscarinic antagonist.

19. The method of claim 17 wherein the acetylcholine release enhancing compound is an m4 selective muscarinic antagonist.

20. A kit for treating a cognitive or neurodegenerative disease comprising in separate containers in a single package pharmaceutical compounds for use in combination, in one container a compound in accordance with any one of claims 1 to 13 and in a separate container an acetylcholinesterase inhibitor, said compound and inhibitor each being in a pharmaceutically acceptable carrier and their combined quantities being an effective amount.

21. A kit for treating a cognitive or neurodegenerative disease comprising in separate containers in a single package pharmaceutical compounds for use in combination, in one container an acetylcholine release enhancing compound and in a separate container an acetylcholinesterase inhibitor, said compound and inhibitor each being in a pharmaceutically acceptable carrier and their combined quantities being an effective amount.

22. The kit of claim 21 wherein said acetylcholine release enhancing compound is an m2 selective muscarinic antagonist.

23. The kit of claim 21 wherein said acetylcholine release enhancing compound is an m4 selective muscarinic antagonist.

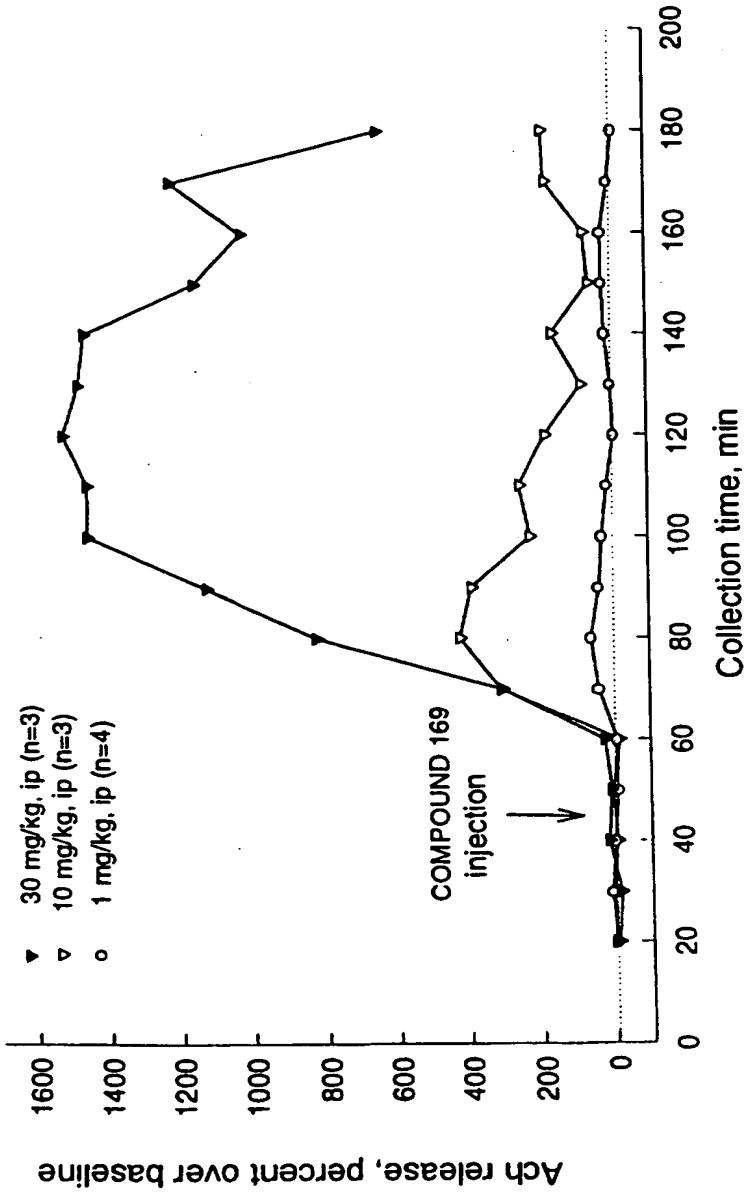

Ach release, percent over baseline
1600
1400
1200
1000
800
600
400
200
0
0
20
40
60
80
100
120
140
160
180
200
Collection time, min
COMPOUND 169
injection
30 mg/kg, ip (n=3)
10 mg/kg, ip (n=3)
1 mg/kg, ip (n=4)

Figure 1

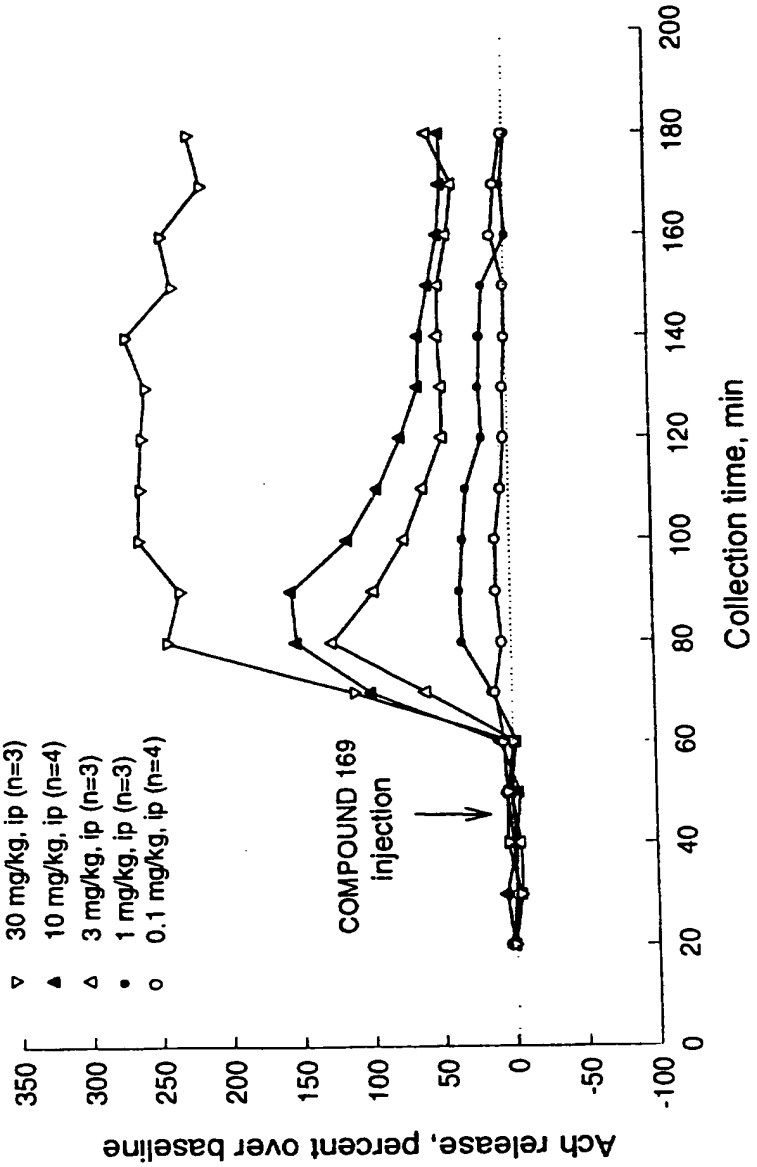

Ach release, percent over baseline
350
300
250
200
150
100
50
0
-50
-100
0
20
40
60
80
100
120
140
160
180
200
Collection time, min
COMPOUND 169
injection
30 mg/kg, ip (n=3)
10 mg/kg, ip (n=4)
3 mg/kg, ip (n=3)
1 mg/kg, ip (n=3)
0.1 mg/kg, ip (n=4)

Figure 2

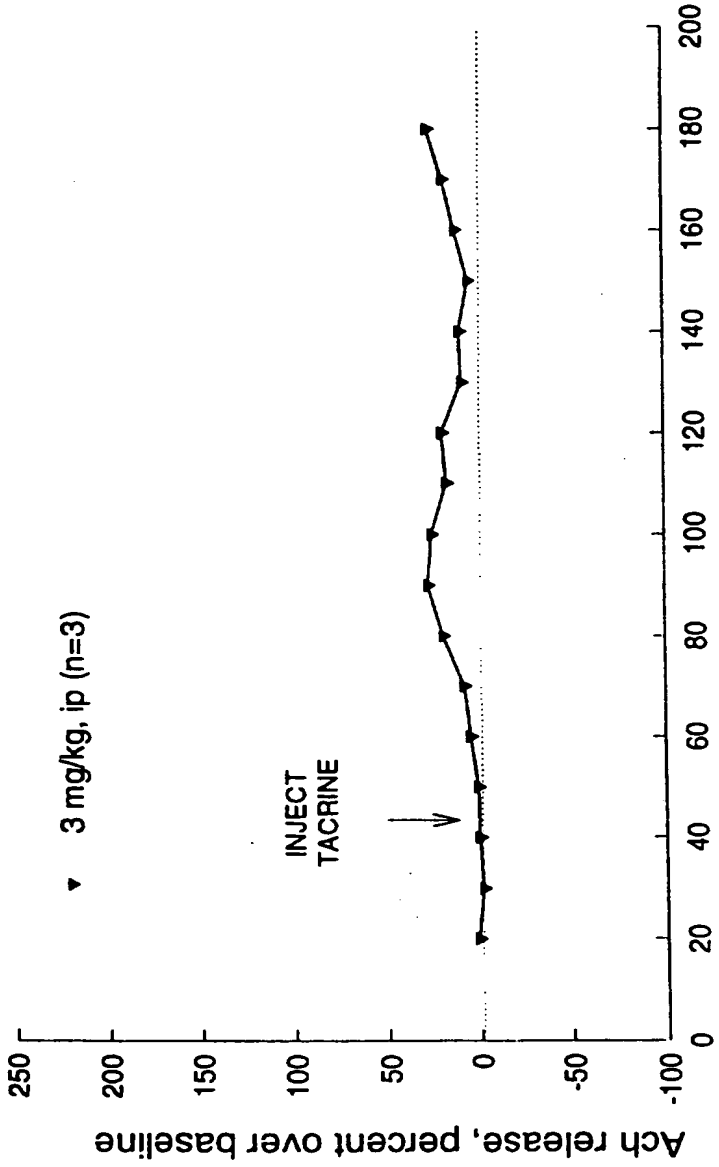

Ach release, percent over baseline
250
200
150
100
50
0
-50
-100
0
20
40
60
80
100
120
140
160
180
200
Collection time, min
INJECT
TACRINE
3 mg/kg, ip (n=3)

Figure 3

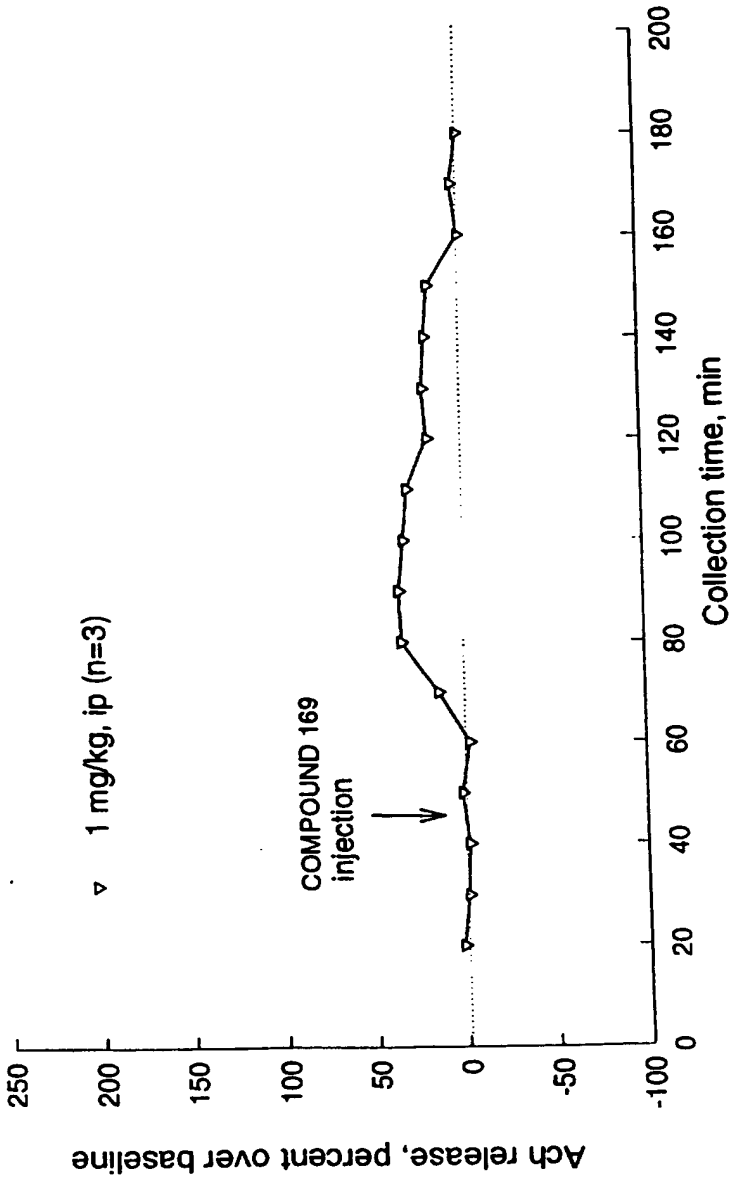

Ach release, percent over baseline
250
200
150
100
50
0
-50
-100
0
20
40
60
80
100
120
140
160
180
200
Collection time, min
COMPOUND 169
injection
1 mg/kg, ip (n=3)

Figure 4

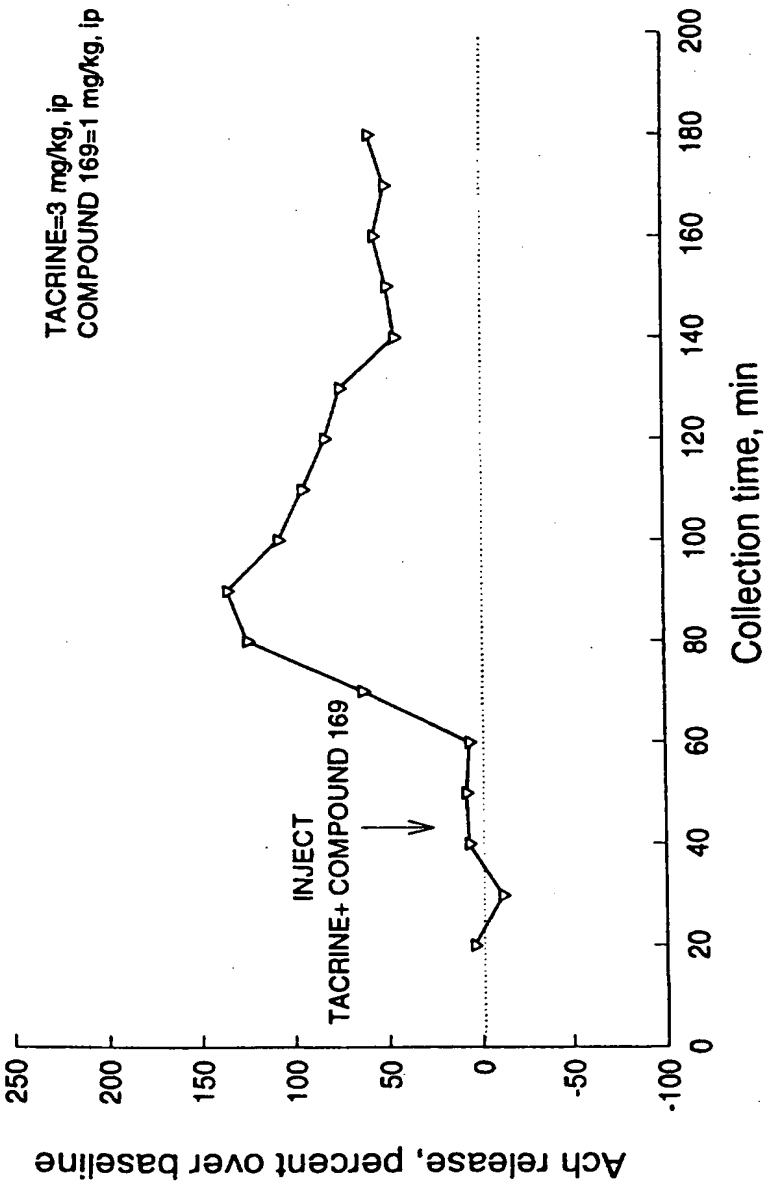

TACRINE=3 mg/kg, ip
COMPOUND 169=1 mg/kg, ip
INJECT
TACRINE+ COMPOUND 169
Ach release, percent over baseline
Collection time, min
250
200
150
100
50
0
-50
-100
0
20
40
60
80
100
120
140
160
180
200

Figure 5

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 295/116, 295/145, A61K 31/445, C07D 401/10, 401/14, 403/10, 407/04, 409/14, 413/10

A3

(11) International Publication Number: WO 96/26196

(43) International Publication Date: 29 August 1996 (29.08.96)

(21) International Application Number: PCT/US96/01532

(22) International Filing Date: 16 February 1996 (16.02.96)

(30) Priority Data:
08/392,697 23 February 1995 (23.02.95) US
08/457,712 2 June 1995 (02.06.95) US

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(74) Agents: LEE, Warrick, E., Jr. et al.; Schering-Plough Corporation, Patent Dept. K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530 (US).

(81) Designated States: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

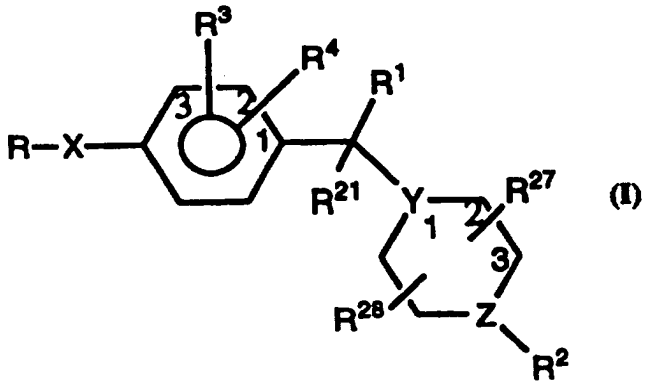
Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
3 October 1996 (03.10.96)

(54) Title: BENZYLPIPERIDINES AND PIPERAZINES AS MUSCARINIC ANTAGONISTS

(57) Abstract

Di-N-substituted piperazine or 1,4 di-substituted piperadine compounds in accordance with formula (I) (including all isomers, salts, esters, and solvates) wherein R, R^1, R^2, R^3, R^4, R^{21}, R^{27}, R^{28}, X, Y, and Z are as defined herein are muscarinic antagonists useful for treating cognitive disorders such as Alzheimer's disease. Pharmaceutical compositions and methods of preparation are also disclosed. Also disclosed are synergistic combinations of compounds of the above formula or other compounds capable of enhan cing acetylcholine release with acetylcholinesterase inhibitors.



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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/01532

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D295/116 C07D295/145 A61K31/445 C07D401/10 C07D401/14
C07D403/10 C07D407/04 C07D409/14 C07D413/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,2 819 273 (T.J. SMITH & NEPHEW LIMITED) 7 January 1958 see claims 2,4 ---	1-11
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X	DE,B,963 424 (DR. KARL THOMAE GMBH) 22 November 1956 * Examples * ---	1-11
X	GB,A,840 358 (BRITISH DRUG HOUSES, LIMITED) 6 July 1960 * Examples * --- -/--	1-11

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Date of the actual completion of the international search	Date of mailing of the international search report
23 July 1996	14.08.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Herz, C

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INTERNATIONAL SEARCH REPORT

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PCT/US 96/01532

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

ernational Application No
PCT/US 96/01532

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 585 500 (MERRELL DOW PHARMACEUTICALS INC.) 9 March 1994 see page 1, line 34 - page 1, line 39; claims 1-12	1-23
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1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/01532

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-11, 14-23
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
please see attached sheet!

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US96/01532

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Lack of conciseness

The breadth of the claims is so large and encompasses too broad a range of totally different chemical groups, only supported to a very limited extent by examples given in the descriptive part of the application. The vast number of theoretically conceivable compounds resulting from the combination of all claimed substituents precludes a comprehensive search. Guided by the inventive concept as disclosed in the descriptive part of the present application a complete search has been limited to Claims 12 and 13. Claims 1 to 11 and 14 to 23 are only searched as far as the specific examples disclosed in the application are concerned

(c.f. Articles 6, 15 and Rule 33 PCT, Guidelines Exam. Part B, Chapt. III, 3.6, 3.7).

INTERNATIONAL SEARCH REPORT

Information on patent family members

ernational Application No
PCT/US 96/01532

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